A Molecular docking study to predict enantioseparation of some chiral carboxylic acid derivatives by methyl-β-cyclodextrin

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Abstract. A molecular docking study, using molecular mechanics calculations with Arguslab, was used to help predict the enantioseparation of some guest molecules of chiral carboxylic acid derivatives by heptakis-2,6-di-O-methyl-β-cyclodextrin (DIMEB) and heptakis-2,3,6-tri-O-methyl-β-cyclodextrin (TRIMEB) as host molecules. The small differences in the binding free energy values (∆∆G) obtained from Arguslab did not indicate any significant enantioseparation. From the molecular docking simulation results, it is predicted that in the case of DIMEB as host molecule, R-enantiomer of Etodolac, Fenoprofen, Indoprofen, Ketorolac, and Naproxen will be eluted first than S-enantiomer; However, S-enantiomer of Carprofen, Flurbiprofen, Ketoprofen, Pirprofen, Proglumide, Sulindac, Surprofen, and Zaltoprofen will be eluted first than R-enantiomer by DIMEB as host molecule. When TRIMEB is used as a host molecule, R-enantiomer of Carprofen, Flurbiprofen, Indoprofen, Ketoprofen, Naproxen, Pirprofen, and Surprofen will be eluted first than S-enantiomer; However, S-enantiomer of Etodolac, Fenoprofen, Ketorolac, Proglumide, Sulindac and Zaltoprofen will be eluted first than R-enantiomer by TRIMEB as host molecule.

1. Introduction

α-, β-, γ-cyclodextrin (CD) are cyclic structure of oligosaccharides, consecutively containing 6, 7, 8 units of D-glucose obtained by enzymatic reaction of starch degradation [1]. All of these cyclodextrin varieties like sliced cone and have amphiphilic property with hydrophobic cavity formed by C-H groups with O4, O5 atoms and hydrophylic side formed by O6-H groups at narrow side and O2-H, O3-H groups at wider side as shown in Figure 1. These cyclodextrins have similar cavity thickness of 7.8 Å but difference in cavity diameter of 6, 8 and 10 Å, respectively. Cyclodextrin has well known for the inclusion ability [2] that has potential alication in the part of industries utilities [3], especially in pharmacy industry [4]. Methyalted on group of O2-H, O6-H or O2-H, O3-H, O6-H which H atom linked to O atom substituted by methyl group, these cyclodextrins become more hydrophobic, e.g.
heptakis(2,6-di-O-methyl)-β-CD (DIMEB) or heptakis(2,3,6-tri-O-methyl)-β-CD (TRIMEB) as shown in Figure 1.

![2D structure of α-, β-, γ-cyclodextrin, DIMEB, and TRIMEB](image)

|        | R₁ = R₂ = H | R₁ = CH₃, R₂ = H | R₁ = R₂ = CH₃ |
|--------|-------------|------------------|--------------|
| Height (Å) | 7.8         | 10.8             | 10.8         |
| Diameter (Å) | 6, 8, 10    | 8                | 8            |

**Figure 1.** a) The 2D structure of α-, β-, γ-cyclodextrin, DIMEB, and TRIMEB [5,6]; (b) The 2D structure of carboxylic acid derivative compounds [6,7]

In addition, methylation process at cyclodextrin will cause the cavity is thicker by 3 Å, and methylated cyclodextrin is less symetric and tend to has better inclusion ability [5,7].

Carboxylic acid derivative compounds are commonly used as anti-inflammatory, antipyretic, analgesic drugs. Most of these compounds are chiral and the properties of chirality affect pharmacology activities [8–13]. It has been reported that S-enantiomer activity of arylpropionate acid derivatives has better pharmacology activity than R-enantiomer, suggesting the importance of a separation technique to collect the S-enantiomer. One of the separation methods for enantioseparation of carboxylic acid derivatives is carried out by HPLC method. In this method, the CSP has very important role in enantioseparation. Many varieties of CSP have been utilized to separate both of these enantiomers [14–17]; most of them are polysaccharide based CSP [18–23].

However, as our best knowledge, the use of DIMEB and TRIMEB based CSP to separate carboxylic acid derivative enantiomers have not been reported elsewhere. Additionally, the mechanism and microscopic phenomena accompanying the separation process of carboxylic acid derivative enantiomers have not been well understood. One way to study this process is by utilizing molecular modeling. At present, there are many molecular modeling methods that can be used to
simulate supramolecular system as inclusion complex modeling between host molecule, β-cyclodextrin and its derivatives with guest molecule, such as: molecular mechanics [24,25], molecular dynamics [26–28], semiempirical methods (such as AM1, PM3) [29–35], ONIOM hibrid, DFT, and DFT-D [36–45]. Among these methods, molecular mechanics is a cheaper alternative for modeling inclusion complex between host and guest molecule. Molecular docking is one of methods using molecular mechanics principles. Some researchers have successfully modeled enantioseparation of guest molecule with host molecule, β-cyclodextrin derivatives, using molecular docking [31, 46–53].

In this research, we modeled the inclusion complex molecule between host molecule, DIMEB and TRIMEB, with guest molecule of enantiomer of carboxylic acid derivative compounds such as Carprofen, Etodolac, Fenoprofen, Flurbiprofen, Indoprofen, Ketoprofen, Ketorolac, Naproxen, Pirprofen, Proglumida, Sulindac, Surprofen, and Zaltoprofen for modeling enantioseparation of carboxylic acid derivative compounds by DIMEB and TRIMEB based CSP. The purpose of this research was to predict qualitatively which enantiomer will be eluted first and which one will be restrained on CSP, as the initial research to explain whether DIMEB and TRIMEB based CSP have potential or not to separate enantiomer of carboxylic acid derivative compounds.

2. Methods
For simplified the calculation, it was assumed that the guest molecule of enantiomer of carboxylic acid derivative compounds only bind in the cavity of host molecule of DIMEB and TRIMEB. However, this assumption still contradictory because in some case, enantioseparation may occur at the outside of the cavity of the host molecule [54–56].

The initial geometry of enantiomer of carboxylic acid derivatives compounds was constructed with Avogadro version of 1.1.1 [57]. Enantiomer of carboxylic acid derivatives were used in this research such as: R/S-Carprofen, R/S- Etodolac, R/S- Fenoprofen, R/S-Flurbiprofen, R/S-Indoprofen, R/S- Ketoprofen, R/S-Ketorolac, R/S-Naproxen, R/S-Pirprofen, R/S-Proglumida, R/S-Sulindac, R/S-Surprofen, dan R/S- Zaltoprofen. The enantiomer geometries of carboxylate acid derivatives compounds were optimized with quantum semiempiric, PM3 method, implemented in Gaussian 09 version of D.01 program package [58].

The initial geometry of host molecule of DIMEB and TRIMEB were also constructed with Avogadro version of 1.1.1 [57] using modified β-cyclodextrin by replacing H atom at position of O2 and O6 with methyl group for DIMEB: replacing H atom at position of O2, O3 and O6 with methyl group for TRIMEB. Both of DIMEB and TRIMEB host molecule were also optimized using quantum semiempiric, PM3 method implemented in Gaussian 09 version of D.01 program package [58].

In order to obtain stable structure of inclusion complex between host and guest molecules, it was taken docking molecular simulation between optimized structures of enantiomer compounds of carboxylate acid derivatives guest molecule and DIMEB and TRIMEB host molecule using ArgusLab version of 4.0.1 program package [59]. There are many researchers using Arguslab program package to perform molecular docking simulation of inclusion complex between cyclodextrin and guest molecule [46–53]. In this molecular docking simulation, the guest molecule of enantiomer of carboxylic acid derivatives was treated as ligand and host molecule of DIMEB and TRIMEB was treated as binding site. This molecular docking simulation used AScore scoring function, binding site box size for host molecule of 20 Å x 20 Å x 20 Å, with grid resolution of 0.4 Å, docking engine of ArgusDock with high precision, no augmented torsions, flexible ligand with maximum number of poses of 200.

3. Results and Discussion
All of inclusion complex from molecular docking simulation result has negative value of $\Delta G$ (binding energy), from -4.38 till -3.54 kcal/mol with frequency between 9.3% till 55%. The negative value of $\Delta G$ indicates that the formed inclusion complex is stable. The difference value of G ($\Delta \Delta G$) was used to learn about the ability of enantioseparation of carboxylic acid derivative compounds using DIMEB and TRIMEB as host molecule. The values of $\Delta \Delta G$ are in the range of -0.08 to 0.04 kcal/mol. Based
on molecular docking simulation result, the value of \( \Delta \Delta G \) indicated that the host molecule of DIMEB and TRIMEB could separate R dan S enantiomer of carboxylic acid derivative compounds. The greater the value of \(| \Delta \Delta G | \) (absolute value of \( \Delta \Delta G \)), the better enantioseparation of guest molecule by host molecule are. Based on molecular docking simulation result, in the case of DIMEB as host molecule, the order of enantioseparation of carboxylic acid compound derivatives separated by DIMEB, from the best to the worst, i.e. Sulindac > Indoprofen > Etodolac > Ketroloac > Carprofen > Naproxen > Zaltoprofen > Fenoprofen > Proglumide > Ketoprofen > Flurbiprofen > Pirprofen > Surprofen. However in the case of TRIMEB as host molecule, the order of enantioseparation of carboxylic acid compound derivatives separated by TRIMEB, from the best to the worst, i.e. Proglumide > Etodolac > Sulindac > Ketoprofen > Zaltoprofen > Flurbiprofen > Indoprofen > Surprofen > Pirprofen > Fenoprofen > Carprofen > Naproxen > Ketroloac.

From the result of molecular docking simulation, based on the value of \( \Delta \Delta G \), it can be predicted that both DIMEB and TRIMEB have differences in the ability to separate enantiomer of carboxylic acid compound derivatives. R/S-Carprofen, R/S-Fenoprofen, R/S-Indoprofen, R/S-Ketoprofen, and R/S-Naproxen, is better separated by DIMEB than TRIMEB, R/S-Etodolac, R/S-Flurbiprofen, R/S-Ketoprofen, R/S-Pirprofen, R/S-Proglumide, R/S-Sulindac, R/S-Surprofen, and R/S-Zaltoprofen is better separated by TRIMEB than DIMEB.

If it was known that the host-guest inclusion complex formation follows the following equation:

\[
\text{Host} + \text{Guest} \rightleftharpoons \text{HostGuest}
\]

(1)

as the equilibrium was reached, the rate of host-guest inclusion complex formation \((v_1)\) will be similar with the rate of host-guest inclusion complex dissociation \((v_{-1})\)

\[
v_1 = v_{-1}
\]

(2)

\[
k_1[\text{Host}]^x[\text{Guest}]^y = k_{-1}[\text{HostGuest}]^z
\]

(3)

\[
\frac{k_1}{k_{-1}} = \frac{[\text{HostGuest}]^z}{[\text{Host}]^x[\text{Guest}]^y}
\]

(4)

\[
K = \frac{k_1}{k_{-1}}
\]

(5)

Where the value of \(K\) was the equilibrium constant of host-guest inclusion complex formation. If \(v_1 \gg v_{-1}\), then \(K \approx k_1\). If it was known that \(v = k \approx 1/t\), then

\[
K \approx \frac{1}{t_1}
\]

(6)

It was known that

\[
\Delta G = -RT \ln K
\]

(7)

and the value of \(\alpha\) is defined by

\[
\alpha \approx \frac{t_R}{t_S}
\]

(8)

where \(t_R\) was migration time of R-enantiomer ant \(t_S\) was migration time of S-enantiomer, then

\[
|\Delta \Delta G| = \Delta G_S - \Delta G_R
\]

(9)

\[
|\Delta \Delta G| = -RT \ln K_S - (-RT \ln K_R)
\]

(10)
\[ |\Delta\Delta G| = -RT \ln K_S + RT \ln K_R \]  \hspace{1cm} (11)

\[ |\Delta\Delta G| = -RT (\ln K_S - \ln K_R) \]  \hspace{1cm} (12)

\[ |\Delta\Delta G| = -RT \left( \frac{1}{t_S} - \frac{1}{t_R} \right) \]  \hspace{1cm} (13)

\[ |\Delta\Delta G| = -RT \left( \frac{t_R}{t_S} \right) \]  \hspace{1cm} (14)

\[ |\Delta\Delta G| = -RT \ln \alpha \]  \hspace{1cm} (15)

Based on the equation (15), it can be calculated the prediction value of separation factor, \( \alpha \), from molecular docking simulation result, where

\[ \alpha = e^{-|\Delta\Delta G|/RT} \]  \hspace{1cm} (16)

Using equation (16), it can be predicted that the separation factor value for enantioseparation of Carprofen, Etodolac, Fenoprofen, Flurbiprofen, Indoprofen, Ketoprofen, Ketorolac, Naproxen, Pirprofen, Proglumide, Sulindac, Surprofen, Zaltoprofen using DIMEB as host molecule is 0.9620, 0.9345, 0.9782, 0.9888, 0.9336, 0.9832, 0.9354, 0.9743, 0.9961, 0.9794, 0.9158, 0.9964, 0.9747, respectively. However, in the case of TRIMEB as host molecule, the value of separation factor for enantioseparation of Carprofen, Etodolac, Fenoprofen, Flurbiprofen, Indoprofen, Ketoprofen, Ketorolac, Naproxen, Pirprofen, Proglumide, Sulindac, Surprofen, Zaltoprofen is 0.9835, 0.9005, 0.9807, 0.9554, 0.9598, 0.9439, 0.9967, 0.9912, 0.9793, 0.8801, 0.9110, 0.9775, 0.9526, respectively.

The positive value of \( \Delta\Delta G \) indicate that the elution rate of R-enantiomer is faster than S-enantiomer, and vice versa, the negative value of \( \Delta\Delta G \) indicate that the elution rate of S-enantiomer is faster than R-enantiomer. Based on the value of \( \Delta\Delta G \), in the case of DIMEB as host molecule, R-enantiomer of Etodolac, Fenoprofen, Indoprofen, Ketoprofen, and Naproxen will be eluted first than S-enantiomer of it, and S-enantiomer of Carprofen, Flurbiprofen, Ketoprofen, Pirprofen, Proglumide, Sulindac, Surprofen, and Zaltoprofen will be eluted first than R-enantiomer of it. However, in the case of TRIMEB as host molecule, R-enantiomer of Carprofen, Flurbiprofen, Indoprofen, Ketoprofen, Naproxen, Pirprofen, Surprofen will be eluted first than S-enantiomer of it, and S-enantiomer of Etodolac, Fenoprofen, Ketorolac, Proglumide, Sulindac, Zaltoprofen will be eluted first than R-enantiomer of it.

The orientation of guest molecule in the inclusion complex is at cavity of DIMEB and TRIMEB, except for inclusion complex of R/S-Sulindac with DIMEB and TRIMEB, where the carboxylic moiety is located at either wider or narrower cavity of DIMEB and TRIMEB. Wider cavity is cavity where O2 and O3 atoms of \( \beta \)-cyclodextrin are located, whereas narrow cavity is cavity where O6 atoms of \( \beta \)-cyclodextrin are located. O2, O3, and O6 is oxygen atom attached to carbon atom at position 2, 3, and 6, respectively, as shown in Figure 1.

Molecular docking simulation result showed that the \( \Delta G \) value of inclusion complex between carboxylic acid derivatives with DIMEB and TRIMEB has very small value or insignificant difference because in molecular docking simulation, the host molecule of DIMEB and TRIMEB was modeled as rigid structure, only the guest molecule was modeled as flexible structure [60]. Therefore, the simulation method must be upgraded to the higher theory level with good cost performance that has better accuracy and less calculation time consuming. One of such method is quantum semiempirical method. The structure of inclusion complex from molecular docking simulation result must be further optimized using quantum semiempirical method, especially PM3 method, to obtain the molecular and thermodynamic properties of inclusion complex more accurately.
4. Conclusions
Based on the molecular docking simulation result, it can be concluded that DIMEB and TRIMEB has ability to separate the enantiomer of carboxylic acid derivative compounds, where R-enantiomer of Etodolac, Fenoprofen, Indoprofen, Ketorolac, Naproxen will be eluted first than S-enantiomer of it, and S-enantiomer of Carprofen, Flurbiprofen, Ketoprofen, Proglumide, Sulindac, Zaltoprofen will be eluted first than R-enantiomer of it in the case of DIMEB as host molecule. However, in the case of TRIMEB as host molecule, R-enantiomer of Carprofen, Flurbiprofen, Indoprofen, Ketoprofen, Naproxen, Pirprofen, Surprofen will be eluted first than S-enantiomer of it, and S-enantiomer of Etodolac, Fenoprofen, Proglumide, Sulindac, Zaltoprofen will be eluted first than R-enantiomer of it.

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