Computational modeling of inclusion complex of r/s-omeprazole with β-cyclodextrin using oniom2 method

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Abstract. Host-guest inclusion complexes between R/S-omeprazole and β-cyclodextrin has been modeled using ONIOM2 (B3LYP/6-31g(d):PM3) method. Based on the value of binding energy obtained from the computational modeling, it was found that inclusion complex of R-omeprazole with β-cyclodextrin is more stable than the inclusion complex of S-omeprazole with β-cyclodextrin, moreover R/S-omeprazole can form stable inclusion complex with β-siklodekstrin by ratio of host : guest equal to 2 : 1. Based on the value of thermodynamic parameters, the formation of inclusion complex between R/S-omeprazole with β-cyclodextrin is an enthalpy driven process.

1. Introduction

Cyclodextrin is a cyclic-organic compound derived from starch transformation through enzymatic process. Cyclodextrin is widely used in many application due to its ability in forming inclusion complex with various large sized molecules [1–3]. Even though the main application of cyclodextrin is in the field of pharmacy, cosmetics, food, and agrochemical industry, cyclodextrin can also used in analytical chemistry application, especially in chiral compounds separation [4–6]. For example, cyclodextrin can be used as CSP in HPLC and CS in CE for S-omeprazole enantiomer separation from R-omeprazole and its racemic mixture [7].

By reducing gastric acid production, omeprazole is widely used to cure syptoms/syndromes caused by excess gastric acid, i.e. GERD (gastroesophageal reflux disease), peptic ulcer, dan Zollinger–Ellison syndrome [8]. This compound with IUPAC name 5-metoksi-2-[(4-metoksi-3,5-dimetilpiridin-2-il)metilsulfinil]-1H-benzimidazol, has molecular structure composed of a substituted pyridine ring attached to benzimidazole through sulphoxide group [9]. The chiral center of this compound located in the sulphoxide group as shown in Figure 1.
In nature, omeprazole exist as two enantiomers: S-enantiomer and R-enantiomer. However, S-omeprazole has higher effectiveness in curing the syndrome compared with R-omeprazole and its racemic mixture [9]. Meanwhile, omeprazole is normally obtained as rasemic mixture. Therefore, a certain method is needed to obtain a more effective drug (S-omeprazole), either by asymmetric synthesis or by enantiomer separation [10]. S-omeprazole can be separated from R-omeprazole by using HPLC (High Performance Liquid Chromatography) or CE (Capillary Electrophoresis). HPLC employed CSP (Chiral Stationary Phase), while CE utilize CS (Chiral Selector) to obtain S-omeprazole from its rasemic mixture.

Some researcher have been doing experimental research about host-guest inclusion complex and reported the results, especially the inclusion complex between R/S-omeprazole with β-cyclodextrin [6,7,9-13]. However, due to the limitations of experimental method, molecular modelling can be used as alternative solution to predict and to explain experimental findings related to chiral recognition by β-cyclodextrin. Nowadays, various theories have been used by researchers to model host-guest inclusion complex, especially inclusion complex between a certain guest molecule and cyclodextrin host molecule. Among those theories, molecular mechanics [14,15], molecular dynamics [16-19], semiempirical methods (such as AM1, PM3) [20-22], hybrid ONIOM method [23-26], have been widely used by researchers to make a model of the inclusion complex between guest molecule and cyclodextrin (and its derivative) host molecule. The calculation method that is most frequently used i.e. hybrid ONIOM method developed by Morokuma et al. [23,24], because hybrid ONIOM method have a good accuracy as well as lower computational cost compared with ab initio and DFT methods. Most of researchers modeled host-guest inclusion complex with ratio host : guest = 1 : 1. However, Rajendiran et al [27] reported that omeprazole and β-cyclodextrin are able to form inclusion complex with ratio of host : guest = 2 : 1 experimentally. Rajendiran et al has not futher investigate about this inclusion complex formation using molecular modeling.

In this research, the interaction in the inclusion complex of R/S-omeprazole with β-siklodekstrin was studied using ONIOM (B3LYP/6-31g(d):PM3) method. The purposes of this research were to found the reason why and how chiral recognition of R/S-omeprazole by β-cyclodextrin occured, and to investigate the main driving force that lead to the inclusion complex formation, also to explain and obtain better understanding about the results reported by Rajendiran et al. In order to study chiral recognition mechanism of R/S-omeprazole by β-cyclodextrin, interaction energy between R/S-omeprazole with β-cyclodextrin was first determined using PM3 method, then continued with ONIOM (B3LYP/6-31g(d):PM3) method to observe interaction energy difference between R-omeprazole with β-cyclodextrin and S-omeprazol with β- cyclodextrin.

2. Computational details
In this molecular modelling, β-cyclodextrin act as host molecule and omeprazole enantiomers act as guest molecule. The structures of β-cyclodextrin used in this research were CD-HH, CD-HT, CD-TT, and CD. CD-HH is a symbol for β-cyclodextrin dimer in which 2'-hydroxyl and 3'‐ hydroxyl functional group in both β-cyclodextrin facing one another forming 180° angle towards the origin of Cartesian coordinate. CD-TT is a symbol for β-cyclodextrin dimer in which 6'-hydroxyl functional group in both β-cyclodextrin facing one another forming 180° angle towards the origin of Cartesian coordinate. CD-HT is a symbol for β-cyclodextrin dimer in which 6'-hydroxyl functional group in one β-cyclodextrin facing with 2'-hydroxyl and 3'‐ hydroxyl functional group in another β-cyclodextrin forming 180° angle towards the origin of Cartesian coordinate.

Each guest and host molecule was optimized using PM3 method with quantum mechanics Gaussian 09 Rev. D.01 [28] software until all eigen values from Hessian matrix were positive. The optimized structure of guest and host molecule then used for docking calculations using Autodock ver 4.2 [29]. The resulting inclusion complex structures from docking calculation were calculated with...
Gaussian 09 Rev. D.01 using semiempiric PM3 method in vacuum (gas phase) condition. Several model sample structures from docking step were calculated using PM3 method, that is sample structure with minimum energy and sample structure with the most frequencies. The resulting optimized structures were further optimized with ONIOM method where β-cyclodextrin molecules which has structure CD, CD-HH, CD-HT, and CD-TT treated as low layer (calculated using PM3 method) and R/S-omeprazole molecule treated as high layer (calculated using DFT method with B3LYP exchange correlation functional and basis set of 6-31g(d)). Analysis of ONIOM (B3LYP/6-31g(d) : PM3) calculation results was performed by involving ∆E (binding energy), ∆H, ∆G, ∆S analysis, DEF (Deformation Energy) guest and host molecule, HOMO energy, LUMO energy, energy gap between HOMO and LUMO, μ (chemical potential), ω (electrophilicity), dipole moment, χ (electronegativity), η (hardness), Mulliken charges, and molecular orbital analysis to obtain further information about the character of the inclusion complexes between R/S-omeprazole with β-cyclodextrin.

3. Results and discussions

ONIOM2 method has been used by several researchers to model host-guest inclusion complexes. This method has relative low cost with good level of accuracy [23-26]. Shi et. al. [26] modeled the inclusion complex between ethyl-3-hydroxybutyrate with permethylated β-cyclodextrin using ratio of host : guest = 1 : 1. The modeling was carried out using quantum semiempiric PM3 method which is further calculated using ONIOM2 method. In ONIOM2 method performed by Shi et. al., guest molecule of ethyl-3-butyrate treated as high layer using DFT method with B3LYP as exchange correlation functional, while host permethylated β-cyclodextrin treated as low layer using quantum semiempiric PM3 method.

The result of ONIOM2 calculation indicate that one unit of β-cyclodextrin in CD-TT-R-OMZ and CD-TT-S-OMZ inclusion complex were distorted. Before the formation of inclusion complex occured, both β-cyclodextrin unit in CD-TT conformation were facing one another forming 180° angle towards the origin of Cartesian coordinate. However, after the formation of inclusion complex took place, both β-cyclodextrin unit were not in the same position and angle anymore. When guest R/S-omeprazole molecule forming inclusion complex with all β-cyclodextrin conformations, the geometry of R/S-omeprazole will undergo several changes. Changes on geometry of R/S-omeprazole can be seen from the shift in structure parameters as shown by Table 1.

The conformation of R/S-omeprazole undergo significant changes during the formation of inclusion complexes, where the molecule of R/S-omeprazole form a specific conformation to form the most stable inclusion complex with host molecule of CD, CD-HH, CD-HT, and CD-TT. These conformation changes in R/S-omeprazole structure indicate that R/S-omeprazole guest molecule tend to be flexible when entering the cavity of β-cyclodextrin in the inclusion complex formation process. According to research reported by Rekharsky et. al. [30], the flexibility of guest and host molecule is one of the important factor leading to the inclusion complex formation because host and guest molecule are able to adjust its conformation in such a way to ensure the inclusion complex formation and to increase entropy of host-guest inclusion complex formation. Based on the shift in interatomic distances and bond angles for atoms listed in Table 1, it can be inferred qualitatively that R-omeprazole was more flexible than S-omeprazole when forming the inclusion complex with β-cyclodextrin.
| Distance between atoms | FREE OMZ | CD-R-OMZ | CD-HH-R-OMZ | CD-HT-R-OMZ | CD-TT-R-OMZ | CD-S-OMZ | CD-HH-S-OMZ | CD-HT-S-OMZ | CD-TT-S-OMZ |
|------------------------|----------|----------|-------------|-------------|-------------|----------|-------------|-------------|-------------|
|                        | R-OMZ    | S-OMZ    | R-OMZ       | R-OMZ       | R-OMZ       | OMZ      | OMZ         | OMZ         | OMZ         |
| C21-C25                | 14.798   | 14.798   | 14.854      | 14.488      | 14.866      | 15.005   | 14.779      | 14.808      | 14.925      | 14.849      |
| C4-C10                 | 4.111    | 4.111    | 4.104       | 4.085       | 4.109       | 4.122    | 4.069       | 4.106       | 4.107       | 4.09        |
| C21-C10                | 8.247    | 8.247    | 8.175       | 8.202       | 8.222       | 8.21     | 8.058       | 8.156       | 8.209       | 8.252       |
| C3-C25                 | 9.066    | 9.066    | 9.115       | 9.14        | 9.185       | 9.304    | 9.134       | 9.214       | 9.243       | 9.074       |
| C3-C10                 | 2.725    | 2.725    | 2.75        | 2.734       | 2.747       | 2.797    | 2.767       | 2.765       | 2.756       | 2.69        |

| Angle (°)              |          |          |             |             |             |          |             |             |             |
| C3-S1-C10              | 95.542   | 95.542   | 97.012      | 96.21       | 97.332      | 99.128   | 97.580      | 97.916      | 97.772      | 94.593      |
| N11-C10-S1             | 127.65   | 127.65   | 126.495     | 126.612     | 125.832     | 127.478  | 127.233     | 127.806     | 126.069     | 127.382     |
| C4-C3-S1               | 110.27   | 110.27   | 107.605     | 110.348     | 108.463     | 106.594  | 105.432     | 106.573     | 107.617     | 110.224     |

| Dihedral (°)           |          |          |             |             |             |          |             |             |             |
| N11-C10-S1-C3          | 64.05    | 64.05    | 64.575      | 56.649      | 58.222      | 61.981   | 65.702      | 50.141      | 62.642      | 71.032      |
| C10-S1-C3-C4           | 177.89   | 177.89   | 177.248     | 160.815     | 179.543     | 168.435  | 163.314     | 173.736     | 175.421     | 171.242     |
| N12-C10-S1-C3          | 119.33   | 119.33   | 120.818     | 130.612     | 130.237     | 127.438  | 118.916     | 139.787     | 126.662     | 111.308     |
| S1-C3-C4-C5            | 90.42    | 90.42    | 90.593      | 90.462      | 86.732      | 99.505   | 98.632      | 96.033      | 95.044      | 142.543     |
Based on the value of $\Delta E$, $\Delta H$, $\Delta G$, and $\Delta S$ obtained from computational modeling using ONIOM2 method, which is shown by Table 2, several points of conclusions can be inferred, i.e. inclusion complex formed from R-omeprazole with $\beta$-cyclodextrin is more stable than of S-omeprazole; Inclusion complex formed from R/S-omeprazole with $\beta$-cyclodextrin dimer (CD-HH, CD-HT, and CD-TT) is more stable than inclusion complex formed from R/S-omeprazole with monomeric $\beta$-cyclodextrin (CD); formation of inclusion complex between R-omeprazole with $\beta$-cyclodextrin is more exothermic than of S-omeprazole; formation of inclusion complex between R/S-omeprazole with $\beta$-cyclodextrin dimer (CD-HH, CD-HT, and CD-TT) is more exothermic than with monomer of $\beta$-cyclodextrin (CD); even though the values of $\Delta G$ formation were positive, the formation of inclusion complex between R-omeprazole and $\beta$-cyclodextrin is more spontaneous than of S-omeprazole at 1 atm and 298.15 K, also the formation of inclusion complex between R/S-omeprazole with $\beta$-cyclodextrin dimer (CD-HH, CD-HT, and CD-TT) is more spontaneous than with monomer of $\beta$-cyclodextrin (CD) at 1 atm and 298.15 K; and formation of inclusion complex between R-omeprazole with $\beta$-cyclodextrin is more favored than S-omeprazole with $\beta$-cyclodextrin because the more positive $\Delta S$ value. Based on $\Delta H$ and $\Delta S$ value obtained from computational modeling using quantum semiempiric PM3 and ONIOM2 method, it was found that the spontaneous formation of inclusion complex R/S-omeprazole is enthalpy driven process because both $\Delta H$ and $\Delta S$ values are negative. These negative values of $\Delta H$ and $\Delta S$ obtained from calculation indicate that the spontanity of complex formation is temperature dependent and the main cause of negative $\Delta G$ value will be the negative value of $\Delta H$.

### 4. Conclusions

The results of computational modeling from this research confirms the research reported by Hancu et al. [31] and Figueiras et al. [11] that the S-enantiomer of omeprazole would be eluted first before the R-omeprazole due to the inclusion complexes of R-omeprazole is more strongly bound to the CSP or CS $\beta$-cyclodextrin compared with the S-omeprazole. This is due to the inclusion complex formed between R-omeprazole with $\beta$-cyclodextrin is more stable, more exothermic, more spontaneous, and more preferably than the inclusion complex of S-omeprazole with $\beta$-cyclodextrin based on the value of $\Delta E$, $\Delta H$, $\Delta G$, $\Delta S$ obtained from the computational modeling. Computational modeling results also confirm the research reported by Rajendiran et al. [27] that the R/S-omeprazole can form stable inclusion complexes with a ratio of host:guest of 2:1. The results of the analysis of thermodynamic parameters such as $\Delta H$ and $\Delta S$ show that the inclusion complex of R/S omeprazole with $\beta$-cyclodextrin has a negative value of $\Delta H$ and $\Delta S$ indicating that the formation of inclusion complex is an enthalpy driven process.

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