Computational study of inclusion complex between Omeprazole enantiomer and β-Cyclodextrin: NBO and RDG analysis

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Abstract. In this study, it has been done NBO and RDG analysis of the R/S-Omeprazole and β-Cyclodextrin inclusion complexes by using density functional theory computational method, one-point calculation with the exchange-correlation functional of B3LYP and basis set of 6-31g (d). The results of the NBO analysis show that there are 7, 52, 5, and 44 of hydrogen bonds in the inclusion complex of β-Cyclodextrin and R-Omeprazole (1:1), β-Cyclodextrin and R-Omeprazole (2:1), β-Cyclodextrin and S-Omeprazole (1:1), and β-Cyclodextrin and S-Omeprazole (2:1), respectively. The results of the RDG analysis confirm that the R/S-Omeprazole inclusion complex with β-Cyclodextrin formed a Van der Waals interaction and also the effect of other than hydrogen bonds. However, the steric effect can be ignored because the amount is relatively small compared to hydrogen bonds and the Van der Waals interactions.

1. Introduction
PPI compound (Proton Pump Inhibitor) is a drug that is used to inhibit the release of excess stomach acid, one of which is Omeprazole. In nature, Omeprazole is present in the form of R/S-Omeprazole enantiomers. However, the S-Omeprazole enantiomer is more effective in curing the disease, so it is necessary to do a separation between the enantiomer R/S-Omeprazole and only S-Omeprazole enantiomer is obtained. The enantiomer separation technique that is commonly used is chromatography. In chromatography, there is a stationary phase which plays an important role in the separation of the enantiomer. One of the most commonly used stationary phases is β-Cyclodextrin. Until now, the mechanism of separation of R/S-Omeprazole enantiomers is still unknown. In 2015, Hancu, et al found experimentally that it turns out that β-Cyclodextrin and Omeprazole can form inclusions with...
comparison of host: guest = 2 : 1 [1]. However, until now there is still no scientific explanation for this phenomenon. Computational studies are one of powerful method that can be used to explain this phenomenon. Several computational methods have been widely used to model host-guest inclusion complexes in various applications to explain scientifically molecular scale phenomena that occur in these inclusion complexes [2-10]. In this research, we will explain the occurrence of this phenomenon through computational calculations with NBO and RDG analysis of the inclusion complex. From the NBO and RDG analysis, it is expected that in the future, a stationary phase that is more effective in separating the R / S-Omeprazole enantiomer can be designed.

2. Methodology

In this research methodology, there are 5 steps to make model and simulate inclusion complex between β-Cyclodextrin and R/S-Omeprazole based on previous research [10].

Step 1. Arranging the input file in the form of 2 hosts molecule of β-Cyclodextrins with configuration: Head-Head, Head-Tail, Tail-Tail and R/S-Omeprazole guests.

Step 2. Docking between host molecules of β-Cyclodextrin and guest R / S-Omeprazole with ratio host: guest = 2 : 1.

Step 3. Geometry optimization of the inclusion complex using PM6.

Step 4. Step 3 is repeated, but by using ONIOM and using the output of Step 3 as input for Step 4.

Step 5. The output from Step 4 is used for NBO and RDG calculations.

3. Results and discussion

The NBO analysis carried out in this study was used to analyze hydrogen bonds formed in the inclusion complex of R/S-oemprazole with β-cyclodextrin. In NBO analysis, electron wave functions are interpreted as occupied Lewis orbitals and unoccupied Lewis orbitals. The interaction due to electron delocalization in the Lewis orbitals can be explained quantitatively by using stabilization energy (Stabilization Energy denoted as $E^{(2)}$), where the value of $E^{(2)}$ is expressed by Equation 1:

$$E^{(2)} = -n_\sigma \frac{\langle \sigma | F | \sigma \rangle}{\epsilon^*_\sigma - \epsilon_\sigma} = -n_\sigma \frac{F_{ij}^2}{\Delta \epsilon} = -n_\sigma \frac{F_{ij}^2}{E_j - E_i}$$

Where $\langle \sigma | F | \sigma \rangle$ or $F_{ij}^2$ is the Fock matrix elements between $i^{th}$ and $j^{th}$ NBO orbitals. $F_{ij}^2$ is the diagonal component of the NBO Fock matrix. $\epsilon^*_\sigma - \epsilon_\sigma$ states the energy of NBO orbitals of $\sigma$ dan $\sigma^*$. $E_j, E_i$ state orbital energy. The value of $E^{(2)}$ can be used to analyze the strength of the hydrogen bonds formed in the host-guest inclusion complex, where at value of $E^{(2)}$ greater than 2.0 kcal/mol for strong hydrogen bonds and $E^{(2)}$ between 0.5 to 2.0 kcal/mol for weak hydrogen bonds.

From the results of the NBO analysis, it was found that in the CD-R-OMZ (β-cyclodextrin and R-omeprazole) inclusion complex there are 7 weak hydrogen bonds with total stabilizing energy ($E^{(2)}$) by the hydrogen bond of 6.76 kcal/mol; in the CD-HH-R-OMZ inclusion complex there are 27 weak hydrogen bonds and 1 strong hydrogen bond with total stabilizing energy ($E^{(2)}$) by the hydrogen bond of 31.17 kcal/mol; in the CD-HT-R-OMZ inclusion complex there are 10 weak hydrogen bonds and 11 strong hydrogen bonds with total stabilizing energy ($E^{(2)}$) by the hydrogen bond of 107.41 kcal/mol; in the CD-TT-R-OMZ inclusion complex there are 4 weak hydrogen bonds with total stabilizing energy ($E^{(2)}$) by the hydrogen bond of 4.34 kcal/mol; in the CD-S-OMZ inclusion complex there are 5 weak hydrogen bonds with total stabilizing energy ($E^{(2)}$) by the hydrogen bond of 4.53 kcal/mol; in the CD-HH-S-OMZ inclusion complex there are 19 weak hydrogen bonds with total stabilizing energy ($E^{(2)}$) by the hydrogen bond of 19.85 kcal/mol; in the CD-HTS-OMZ inclusion complex there are 9 weak hydrogen bonds and 9 strong hydrogen bonds with total stabilizing energy ($E^{(2)}$) by the hydrogen bond of 86.49 kcal/mol; in the CD-TT-S-OMZ inclusion complex there are 7 weak hydrogen bonds with total stabilizing energy ($E^{(2)}$) by the hydrogen bond of 4.75 kcal/mol. The total number of hydrogen bonds in the R-omeprazole inclusion complex with β-cyclodextrin is more, which is 60 hydrogen bonds, when compared with hydrogen bonds in the S-omeprazole inclusion complex with β-cyclodextrin which only
has 49 hydrogen bonds. The total $E^{(2)}$ value for the R-omeprazole inclusion complex is also greater, which is 150.22 kcal/mol, when compared with the total $E^{(2)}$ value in the S-omeprazole inclusion complex with $\beta$-cyclodextrin which is only 115.62 kcal/mol. Thus, it can be concluded that the R-omeprazole inclusion complex with $\beta$-cyclodextrin is more stable which is stabilized by hydrogen bonds formed, when compared with the inclusion complex of S-omeprazole and $\beta$-cyclodextrin.

The NBO analysis also shows that the inclusion complex of R/S-omeprazole and $\beta$-cyclodextrin with host : guest ratio = 2 : 1 has a greater number of hydrogen bonds and the value of $E^{(2)}$ which is greater than the $\beta$-cyclodextrin and R/S-omeprazole inclusion complex with host : guest = 1 : 1. Thus, it can be concluded also that the inclusion complex of R/S-omeprazole and $\beta$-cyclodextrin with host : guest ratio = 2 : 1 is formed more stable compared to inclusion complex with host : guest = 1 : 1.

RDG analysis is done to confirm the presence or absence of interactions between molecules other than hydrogen bonds. The RDG function equation is defined as:

$$RDG(r) = \frac{1}{2(3\pi^2)^{1/2}} \frac{|\nabla \rho(r)|}{\rho(r)^{7/6}}$$  \hspace{1cm} (2)

The results of the RDG analysis confirmed that the inclusion complex of R/S-omeprazole and $\beta$-cyclodextrin formed a Van der Waals interaction and also a steric effect other than hydrogen bonds. However, from the Figure 1, it can be seen that the effect of the steric effect can be ignored because the amount is relatively small compared to hydrogen bonds and Van der Waals interactions. RDG analysis of intermolecular interactions in the inclusion complex of R/S-omeprazole and $\beta$-cyclodextrin is shown in Figure 1.
Figure 1. RDG analysis of inclusion complexes (a) and (b) CYD-R-OMZ, (c) and (d) CYD-HH-R-OMZ, (e) and (f) CYD-HT-R-OMZ, (g) and (h) CYD-TT-R-OMZ, (i) and (j) CYD-S-OMZ, (k) and (l) CYD-HHS-OMZ, (m) and (n) CYD-HT-S-OMZ, (o) and (p) CYD-TT-SOMZ. (Note: For Figures IV.11 (a), (c), (e), (g), (i), (k), (m), and (o), a blue circle indicates a hydrogen bond, a green circle indicates a Van der Waals interaction, and a red circle indicates a steric effect).

4. Conclusion

From the results of the NBO calculation, it was found that the number of hydrogen bonds formed in the complex inclusion between β-Cyclodextrin and guest R / S-Omeprazole with host:guest ratio = 2:1 is greater than the host:guest ratio = 1:1 and analysis results RDG confirms the results of NBO calculations.

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