CHAPTER 6
QM/MM Studies on Cyclodextrin-Alcohol Interaction

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6.1. Introduction

Interaction between the membrane material and the substrate play an important role in adsorption process. Strong interactions (hydrogen bonding or electrostatic) between adsorbent and adsorbate allow the rate of adsorption of alcohols whereas repulsive interactions do not allow the adsorption on the membrane. Thus, understanding the interaction between adsorbent and adsorbate becomes an important factor for designing new adsorbents.

Stachowicz et al. have made DFT studies on cation binding of β-cyclodextrin (CD) [1]. A number of theoretical methods are used in molecular modeling for supermolecular systems such as the complexes of CDs or their derivatives with guest molecules [2-14]. Among these theoretical methods, molecular mechanics (MM) [2, 3], molecular dynamics (MD) [4-7], semi-empirical methods (such as AM1, PM3 etc.) [8-14] and a hybrid Own N-layer Integrated Orbital Molecular Mechanics (ONIOM) methods [15-24] have been widely used for relatively larger sized CDs and their derivatives.

Quantum mechanical methods such as density functional theory are quite useful in understanding the types of interactions in molecular systems (hydrogen bonding and electrostatic in present case). Even though β-CD drew the attention of many researchers, due to its large size only few computational studies have been reported [3].

One of the main aims in computational chemistry is to find a balance between the accuracy of the results and the computational cost. However, the computational costs of accurate methods scale very unfavourably with the size of the system. Molecular mechanics (MM), semi-emperical, and independent particle models such as Hartee-
Fock(HF) or Density Functional Theory (DFT) methods scale linearly, but MP2, MP3, MP4 and MP5 scale $N^5$, $N^6$, $N^7$ and $N^8$ respectively. It is clear that the scaling problem becomes more severe with increasing $N$, and it is often not possible to increase the accuracy of the calculation when large systems are considered. Although linear scaling implementations are available for semi-empirical and DFT methods, they have pre-factors that are too high for (dynamics) calculations on very large systems, and often more accurate methods are needed.

The hybrid methods offer a solution to the scaling problem. Various regions of a system play different roles in a process under investigation. Examples of such cases are, most enzymatic reactions, where the bond breaking and forming take place only in the active site, and the effect of the protein environment is usually only steric or electrostatic. Other examples are processes in solution, where the role of the solute is clearly is treated with a different computational method. It can turns out that expensive computational methods are only required for the part of the system where the action takes place while less expensive methods can be used for the supporting regions. As a result, accurate results can be obtained for a reaction of the computational cost of conventional methods.

Out of these methods, a hybrid ONIOM method, developed by Morokuma et al. [13-15], has been used widely as it can treat different parts of a system simultaneously with good accuracy and lower computational cost compared to ab-initio and DFT, and it has been proved to be effective and reliable for investigating inclusion interaction of CDs or their derivatives with guests molecules [19-22]. MM methods based on classical empirical potentials have been proven to provide an effective mean for simulating complex

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molecules. Alternatively, description of classical reactions (i.e. bond-forming and bond-breaking) and other processes that involve changes in the electronic structure, such as charge transfer or electronic excitation, transition state etc. require QM methods. However, due to high computational cost, QM methods have limitations in case of larger systems. Therefore, it is suitable to use a QM method for the chemically active region and combine it with an MM treatment for the surroundings. By doing this, we can treat a large system into a QM region and a MM region, such that only a small part of the system can be analyzed by the QM method, but still retains the effects of the surrounding environment.

In this chapter, we have aimed to give an insight into the extent of interaction between β-CD and alcohols during adsorption of the alcohols on CD membrane. The emphasis is to interpret the interaction of the alcohols with different centers in CD. Sakurai et al. used CNDO method to CD chemistry [25]. Earlier Lei Liu et al. used AM1 and PM3 methods to study the structures of CD complexes [26]. However, these methods are not useful in estimating the interaction energies. To gain a better understanding on the role of interactions between adsorbate and adsorbent, we used QM/MM methods [27]. This method is widely used to quantify interactions in large systems and their success in this aspect is documented well [28].

6.2. Computational details

The gas phase geometrical minima of the species are optimized using (QM/MM) method. We considered the alcohol and two glucose units in the QM region and applied polarized triple zeta basis set with diffused and polarized functions, 6-311++G(d,p) with Becke three parameter exchange and Lee, Yang and Parr correlation functional, B3LYP
[29, 30] in the QM region. Rest of the glucose units are considered in the MM region and MM force field (PM3) is used in this region. To check the consistency of the calculations, we performed single point calculations at BHandH/631++G(d,p):PM3 level of theory as well. Choice of the basis set is based on the consideration that in order to obtain reliable properties for hydrogen bonded systems, it is essential to employ basis sets that possess sufficient diffuseness and angular flexibility. Vibrational frequency analysis was performed in all cases to ensure that the species possess no imaginary frequency. Interaction energies between three alcohols viz. methanol, ethanol, butanol and cyclodextrin are calculated using supermolecular approach, (for a process $A+B \rightarrow AB$, interaction energy is defined as, $\Delta E_{\text{int}} = E_{AB} - E_A - E_B$), where, $E_A$, $E_B$ and $E_{AB}$ are the energies of the corresponding species), [31]. To observe the thermodynamic driving force, we calculated enthalpy of adducts formation ($\Delta H_{AB} = H_{AB} - H_A - H_B$). All calculations are performed in Gaussian09 [32].

6.3. Results and discussion

Hydrogen bonding interactions have generated substantial interest in the field of chemistry and biology [33]. The formation of molecular complexes is governed by hydrogen bonds and other allied interactions [34-36]. Different types of theoretical parameters like molecular orbital, charge on atoms, bond order, etc are commonly employed to correlate reactivity and stability of molecular systems [37]. The density functional theory (DFT) has been employed successfully to study of hydrogen bonding patterns in different types of molecular systems [38-40]. In surface chemistry, interaction between the membrane material (as adsorbent) and alcohol (as adsorbate) are important. $\beta$-
CD is the most important component of our prepared membrane [41, 42] and it is expected that as the alcohol molecules get adsorbed on the membrane, hydrogen bonds can be formed between the two components, alcohols and β-CD and this interactions might influence adsorption phenomenon.

The oxygen atoms in cyclodextrin molecule provide room for interactions as can be seen from electron density isosurface (Figure 6.1). The red colour indicates the negatively charged region available for interaction in the CD molecule forming a host-guest complex.

Figure 6.1: Electron density isosurfaces of cyclodextrin.

The interaction mainly involves hydrogen bonding between O sites in CD and OH group of the alcohol, and between OH sites in CD and O sites of alcohol. Consequently, we have calculated interaction energies between CD and alcohol molecules using supermolecular approach. Enthalpy involved during interactions are also calculated (\( \Delta H_{AB} = H_{AB} - (H_A + H_B) \)). The optimized structures along with some important parameters (O of CD and H of OH group of alcohol bond lengths, H of CD and O of OH group of alcohol bond lengths, O-H-O bond angles) are presented in Figure 6.2 and gas phase interaction energy and enthalpies are presented in Table 6.1.
QM/MM region in $\beta$-CD

$\beta$-CD-1m, 164.67°, 1.80 Å

$\beta$-CD-2m, 162.46°, 1.82 Å

$\beta$-CD-3m, 148.88°, 2.06 Å

$\beta$-CD-4m, 156.41°, 2.02 Å

$\beta$-CD-5m, 163.53°, 1.87 Å

$\beta$-CD-1e, 164.62°, 1.82 Å
Figure 6.2: Optimized structure of the β-CD and β-CD-alcohol adducts at B3LYP/6-31++G(d,p):PM3 level of theory.
Table 6.1: Gas phase interaction energy $\Delta E_{\text{int}}$(kcal mol$^{-1}$) and $\Delta H$ (kcal mol$^{-1}$) at two different levels of theory.

<table>
<thead>
<tr>
<th>Adducts</th>
<th>$\Delta E_{\text{int}}$</th>
<th>$\Delta H$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(B3LYP/631++G(d,p):PM3)</td>
<td>(BHandH/631++(d,p):PM)</td>
</tr>
<tr>
<td>$\beta$CD-1m</td>
<td>-9.73</td>
<td>-33.86</td>
</tr>
<tr>
<td>$\beta$CD-2m</td>
<td>-5.39</td>
<td>-10.27</td>
</tr>
<tr>
<td>$\beta$CD-3m</td>
<td>-5.31</td>
<td>-9.86</td>
</tr>
<tr>
<td>$\beta$CD-4m</td>
<td>-4.65</td>
<td>-8.98</td>
</tr>
<tr>
<td>$\beta$CD-5m</td>
<td>-5.45</td>
<td>-25.31</td>
</tr>
<tr>
<td>$\beta$CD-1e</td>
<td>-9.35</td>
<td>-32.03</td>
</tr>
<tr>
<td>$\beta$CD-2e</td>
<td>-4.67</td>
<td>-10.17</td>
</tr>
<tr>
<td>$\beta$CD-3e</td>
<td>-5.16</td>
<td>-9.82</td>
</tr>
<tr>
<td>$\beta$CD-4e</td>
<td>-4.37</td>
<td>-8.36</td>
</tr>
<tr>
<td>$\beta$CD-5e</td>
<td>-4.80</td>
<td>-22.51</td>
</tr>
<tr>
<td>$\beta$CD-1b</td>
<td>-9.28</td>
<td>-31.50</td>
</tr>
<tr>
<td>$\beta$CD-2b</td>
<td>-4.59</td>
<td>-10.14</td>
</tr>
<tr>
<td>$\beta$CD-3b</td>
<td>-5.03</td>
<td>-9.78</td>
</tr>
<tr>
<td>$\beta$CD-4b</td>
<td>-4.29</td>
<td>-8.20</td>
</tr>
<tr>
<td>$\beta$CD-5b</td>
<td>-4.62</td>
<td>-21.16</td>
</tr>
</tbody>
</table>

It is observed that the bond length between O-1 of $\beta$-CD with H (in OH group) of methanol, ethanol, and butanol are 1.80 Å, 1.82 Å and 1.83 Å respectively. In O-2, O-3 and O-4 positions, these values are 1.82 Å, 1.82 Å, 1.83 Å (in O-2 position), 2.06 Å, 2.07 Å, 2.07 Å (in O-3 position) and 2.02 Å, 2.02 Å, 1.98 Å (in of O-4 position) respectively.

On the other hand, when we considered the hydrogen bonding between O-atom of OH group (indicated by O-5 in Figure 6.2) of alcohol with H atom of OH group of $\beta$-CD (attached to O-1 position), the observed bond length is 1.87 Å in methanol and 1.88 Å in
ethanol and butanol. Shorter bond lengths in case of O-1, O-2 and O-5 interactions indicate a stronger interaction compared to O-3 or O-4 position and interaction energy values provided in Table 6.1 also reflected the fact. The $\angle$O-H-O bond angles in case of O-1, O-5 and O-2 interactions are observed to be $\sim$165°, $\sim$164° and $\sim$162° respectively. However, in case of O-3 interactions, these values are $\sim$149° and with O-4 centers these values are in the range 152°-156°. Structural parameters play important role in strength of a hydrogen bonding and thus are important [43]. Usually, it is a general observed that a shorter O-H bond length and higher $\angle$O-H-O ($\sim$180°) facilitate a stronger hydrogen bonding. Results agrees well with this fact and we observed stronger hydrogen bonding (higher interaction energy) in case of O-1, O-5 and O-2 interactions where the O-H bond lengths are comparatively shorter and $\angle$O-H-O bond angles are larger (Figure 6.2, Table 6.1).

Interaction energies at different O-centers reveal that the interactions are not so strong. At B3LYP/6-311++G(d,p):PM3 level of theory, interaction energies are observed to be $\sim$ -10 kcal mol$^{-1}$. The order of interaction energies at the four O-centers at both the two levels of theory are observed to be O-1>O-2>O-3>O-4. Steric factor is observed to play a major role on the interactions; O-3 and O-4 positions are sterically hindered and we observe lower interaction energy compared to O-1 and O-2. At BH$\text{and}$H/6-311++G(d,p):PM3 level of theory, the observed values of interaction energies are comparatively higher. These values of interaction energy are important; a stronger interaction favors adsorption, moreover a repulsive interaction makes it difficult for the molecule to be adsorbed on the membrane. Interaction energy at O-5 centre of alcohol is found to be in between to that at O-1 and O-2 centre. The calculated energies tabulated in
Table 6.1 shows consistency in results and clearly depict interactions between the components of adsorbent and adsorbate. Thus, interaction energy implies that the β-CD component of the membrane allow the alcohol components to adsorb. Interestingly the enthalpy gain during the interactions is exothermic, indicating presence of thermodynamic driving force. From Table 6.1, it is observed that the trend of interaction energy is in the order CD-MeOH> CD-EtOH> CD-BuOH. Interaction energy at O-1 position is found to be -9.74 kcal mol$^{-1}$, -9.35 kcal mol$^{-1}$ and -9.28 kcal mol$^{-1}$ for CD-MeOH, CD-EtOH and CD-BuOH respectively at B3LYP/6-311++G(d,p):PM3 level of theory. At BHandH/6-311++G(d,p):PM3 level of theory, the respective values obtained at O-1 position are higher than that in B3LYP/6-311++G(d,p):PM3 level of theory and are -33.86 kcal mol$^{-1}$, -32.03 kcal mol$^{-1}$ and -31.50 kcal mol$^{-1}$ for CD-MeOH, CD-EtOH and CD-BuOH.

In addition, the thermochemical analysis suggests that the interactions are enthalpy driven. The order found in enthalpy follows the same order as in interaction energy and is, CD-MeOH> CD-EtOH> CD-BuOH. At B3LYP/6-311++G(d,p):PM3 level of theory, enthalpy values found to be -4.15 kcal mol$^{-1}$, -3.83 kcal mol$^{-1}$, -3.78 kcal mol$^{-1}$. Similar trend is observed at BHandH/6-311++G(d,p):PM3 level of theory. Enthalpy values obtained at O-1 position at BHandH/6-311++G(d,p):PM3 level of theory are -26.35 kcal mol$^{-1}$, -25.58 kcal mol$^{-1}$ and -24.51 kcal mol$^{-1}$ respectively for CD-MeOH, CD-EtOH, CD-BuOH adducts.

The correlation between interactions energy and experimentally obtained adsorption affinity values are examined. Higher value of interaction energy leads to stronger adsorption [29] and it plays the key role on adsorption. Interaction energy is found
to be an index of the strength of adsorptive interaction on the adsorbent surface. The correlation between experimentally obtained adsorption enthalpy ($\Delta H^\circ$) for three alcohols was plotted against adsorptive interaction energies ($\Delta E_{\text{int}}$) and is shown in Figure 6.3.

![Graph showing interaction energy as a function of change in enthalpy, 1: CD-MeOH, 2: CD-EtOH, 3: CD-BuOH.](image)

**Figure 6.3.** Interaction energy as a function of change in enthalpy, 1: CD-MeOH, 2: CD-EtOH, 3: CD-BuOH.

Figure 6.3 shows a reasonable linear relationship between interaction energy and enthalpy. This implies that the enthalpies of adsorption are in conformity with adsorptive interaction energy. Since the enthalpy is a measure of the strength of the solute–sorbent binding interaction, the correlation shown in Figure 6.3 demonstrates that the strength of the solute-sorbent binding interaction significantly affects the adsorption affinity.

We also examined the relationship between the charge density at the O-centers and interaction energies. We performed Hirshfeld population analysis to estimate charge density at different sites. The charge density at O-1, O-2, O-3, O-4 centers are observed to
be \(-0.177 \text{ au}, -0.166 \text{ au}, -0.148 \text{ au} \) and \(-0.128 \text{ au}\) respectively. This reflects that these positions will exhibit more affinity towards the \(–\text{OH}\) groups in alcohols. Interaction energy is found to be more in \(\text{O-1}\) and \(\text{O-2}\) positions in all the three \(\text{CD-alcohol}\) system. The presence of +I (electron donating group) alkyl groups decrease the electronegativity of etheral type oxygen in \(\text{O-3}\) and \(\text{O-4}\) position. Hence, the hydrogen bonds with these positions are considerably weaker and so, interactions are less compared to that in \(\text{O-1}\) and \(\text{O-2}\) positions. Again, compared to \(\text{O-4}\) position, interaction energy is found to be higher in \(\text{O-3}\) position. The \(\text{O-3}\) center is exposed more due to fluxional of the glucopyranose ring and so, interaction is stronger. On the other hand, \(\text{O-4}\) center is rigid. Similar trend is found in case of enthalpy. It is also observed that the possibility of interaction from the inner core of \(\text{CD}\) is very difficult because of steric hindrance and hydrophobicity.

6.4. Conclusion

Our study reveals the formation of hydrogen bonding between the \(\text{CD}\) and alcohols. An intermediate value of interaction energy indicates that the rate of adsorption is governed by the host-guest interaction. Interaction energy is found to be higher at \(\text{O-1}\) and \(\text{O-2}\) centers of the \(\text{CD}\) and at \(\text{O-5}\) centre of alcohol. In addition, the thermochemical analysis suggests that the formations of these inclusion complexes are enthalpy driven. The overall theoretical studies show that hydrogen bonding play an important role in the adsorption on membrane.
6.5. References


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