Theoretical study of inclusion complexation of tricyclic antidepressant drugs with β-cyclodextrin

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The inclusion process of four tricyclic antidepressant drugs (carbamazepine, imipramine, dothiepin and doxepin) with β-cyclodextrin (β-CD), as well as their possible interaction types have been investigated theoretically. The data suggest that these drugs are partially encapsulated into the β-CD cavity. The formation of the inclusion complex is predicted to be an enthalpy-driven process in gas phase. Different interactions between these drugs and β-CD should be also possible due to their negative binding energy though their distributions differ greatly. Comparative study of the interactions of these drugs with β-CD has been investigated and their obvious differences in binding energy and enthalpy change suggest that the β-CD can identify the stability of the complex.

Keywords: Theoretical chemistry, Cyclodextrin, Tricyclic antidepressant drugs, Inclusion complex, Molecular recognition

Inclusion complexation is the focus of current host–guest chemistry and supramolecular chemistry. Cyclodextrins (CDs), the most prominent host molecules till date are cyclic oligosaccharides composed of glucopyranose units and can be characterized as a truncated cone structure with hydrophobic interior and hydrophilic exterior. Due to the amphiphilic molecular structure of CDs it is easy to form inclusion complexes with several organic, inorganic and biological compounds without covalent bond and the resultant inclusion complexes can induce modification of the physicochemical properties of guest molecules (such as water solubility and solution stability). Therefore pharmaceutical application of CDs as additives and drug-complexing agents had attracted growing attention in many years. In addition, CDs can mediate many organic reactions in which CDs represent a good model of mimicking enzymes and have molecular recognition property to identify the small differences between compounds. Due to the limitations of the experimental methods, in recent times molecular modeling has become very popular in CD chemistry. The studied guest molecules, imipramine (10,11-dihydro-N,N-dimethyl-5H-dibenz[b,f] azepine-5-propamine), carbamazepine (5H-dibenzo[b,f]azepine-5-carboxamide), dothiepin (11(16H)-(3-[dimethyl amino] propylidene) dibenz[b,e] oxepine) and doxepin (11(16H)-(3-[dimethyl amino] propylidene) dibenz[b,e] thiopine) drugs (Fig. 1) are quite large and thus will be encapsulated only partially in the β-CD cavity. In our recent studies, we have experimentally proved that the above molecules were formed 1:2 inclusion complex with β-CD. While it has been reported that carbamazepine is used for grandmal epilepsy and psychomotor seizures treatment and imipramine, dothiepin, doxepin are used as antidepressant, their application in pharmaceutical field is limited by their low aqueous solubility. Hence, CDs are introduced to improve their water solubility. However, the geometrical structure and stability of the complex as well as the inclusion energetics of the formation process between the guest molecule and the CDs host are still not reported theoretically to the best of our knowledge. Here in, the interactions of β-CD with carbamazepine, imipramine, dothiepin and doxepin are studied by quantum methods. We have investigated the geometrical structures and stability of the complexes and discussed the possible interactions between β-CD and the above drugs as shown in Fig. 2. The interactions of β-CD with the above drugs have also been compared.

Computational Methods

The initial structure of β-CD, carbamazepine, imipramine, dothiepin and doxepin were built with Spartan (version 8.0) and fully optimized by PM3
method without imposing any symmetrical restrictions. Since the semiempirical PM3 method has been proved to be a powerful tool in the conformational study of cyclodextrin complexes and has high computational efficiency in calculating the CDs systems\textsuperscript{22–24}, it was selected to study the inclusion process of β-CD with the above drugs.

The glycosidic oxygen atoms of β-CD were placed onto the XY plane and their center was defined as the center of the coordination system. The primary hydroxyl groups were placed pointing toward the positive Z axis. The inclusion complexes were constructed from the PM3-optimized β-CD and guest molecules. The functional groups were always pointing towards the primary hydroxyls of β-CD according to the experimental observation\textsuperscript{19,20}. The longer dimension of the guest molecule was initially aligned with the Z axis. The position of the guest was determined by the Z coordinate of one selected atom of the guest. The inclusion process was simulated by putting the guest on one end of β-CD and then letting it pass through the β-CD cavity by steps. In every step, the geometry of the host-guest complex was completely optimized by PM3 without any restriction. Frequency calculations using PM3 were also performed, and no negative eigen value was found for the final structures. The PM3-optimized host–guest molecular structures of the four complexes are shown in Fig. 2.

HOMO as ionization energy (IE) and LUMO as electron affinity (EA) were used for calculating the electronic chemical potential (µ), which is half of the energy of the HOMO and LUMO:

**Fig. 1**—CAChe structures and bond lengths of (a) carbamazepine, (b) imipramine, (c) dothiepin, and, (d) doxepin. [(a) Carbamazepine: H\textsubscript{1} – H\textsubscript{4} = 4.8964; H\textsubscript{5} – H\textsubscript{9} = 9.2785; H\textsubscript{4} – H\textsubscript{11} = 7.7403; C\textsubscript{1} – C\textsubscript{2} = 8.0328; H\textsubscript{7} – H\textsubscript{10} = 4.8656; C\textsubscript{4} – N\textsubscript{2} = 5.6859; H\textsubscript{1} – H\textsubscript{4} = 10.0516; C\textsubscript{1} – N\textsubscript{2} = 5.8998; C\textsubscript{6} – H\textsubscript{12} = 6.5785; C\textsubscript{2} – C\textsubscript{8} = 7.5894; C\textsubscript{3} – H\textsubscript{12} = 6.6776; H\textsubscript{6} – H\textsubscript{11} = 7.5872. (b) Imipramine: H\textsubscript{1} – H\textsubscript{4} = 4.9832; N\textsubscript{1} – H\textsubscript{24} = 7.0507; H\textsubscript{3} – H\textsubscript{10} = 9.1318; H\textsubscript{4} – H\textsubscript{11} = 4.9538; C\textsubscript{15} – H\textsubscript{24} = 5.8727; C\textsubscript{2} – C\textsubscript{3} = 6.6452; N\textsubscript{1} – N\textsubscript{2} = 4.9559; C\textsubscript{15} – C\textsubscript{19} = 4.9640; N\textsubscript{1} – C\textsubscript{19} = 6.2382; C\textsubscript{4} – C\textsubscript{8} = 7.2558. (c) Dothiepin: C\textsubscript{15} – C\textsubscript{19} = 6.2401; C\textsubscript{4} – C\textsubscript{8} = 7.2294; H\textsubscript{3} – H\textsubscript{8} = 9.0816; C\textsubscript{4} – C\textsubscript{8} = 6.4697; H\textsubscript{1} – H\textsubscript{4} = 4.9641; C\textsubscript{15} – H\textsubscript{21} = 7.0529; H\textsubscript{4} – H\textsubscript{21} = 12.6782; C\textsubscript{4} – C\textsubscript{9} = 10.9510. (d) Doxepin: C\textsubscript{15} – C\textsubscript{19} = 6.2316; C\textsubscript{4} – C\textsubscript{8} = 7.2316; C\textsubscript{3} – C\textsubscript{9} = 6.7384; C\textsubscript{6} – H\textsubscript{12} = 9.0869; C\textsubscript{4} – C\textsubscript{9} = 7.1730; H\textsubscript{1} – H\textsubscript{14} = 4.9917; C\textsubscript{15} – H\textsubscript{21} = 7.0401; C\textsubscript{4} – C\textsubscript{9} = 10.9122; H\textsubscript{4} – H\textsubscript{21} = 12.5929.]
µ = (\(E_{\text{HOMO}} + E_{\text{LUMO}}\))/2 \hspace{1cm} \ldots (1)

The hardness (\(\eta\)) as half of the gap energy between HOMO and LUMO was calculated using the following expression:

\[ \text{Gap} = E_{\text{HOMO}} - E_{\text{LUMO}} \] \hspace{1cm} \ldots (2)

\[ \eta = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \] \hspace{1cm} \ldots (3)

The electrophilicity (\(\omega\)) of the components are calculated in HF method using the following eq. (4):

\[ \omega = \frac{\mu^2}{2\eta} \] \hspace{1cm} \ldots (4)

The complexation energy for the inclusion process was evaluated using eq. (5)

\[ \Delta E_{\text{complexation}} = E_{\text{complex}} - (E_{\beta\text{-CD}} + E_{\text{drug}}) \] \hspace{1cm} \ldots (5)

where \(E_{\text{complex}}\), \(E_{\beta\text{-CD}}\) and \(E_{\text{drug}}\) represent the total energy of the complex, the free optimized \(\beta\text{-CD}\) and the free optimized drugs respectively.

**Result and Discussion**

**HOMO - LUMO parameters**

Table 1 summarizes the energy, HOMO, LUMO, thermodynamic parameters (enthalpy, entropy, free energy), chemical potential (\(\mu\)), stability (\(S\)), dipole moment, hardness (\(\eta\)), electrophilicity (\(\omega\)), zero point vibrational energy and Mulliken charge of the guest (carbamazepine, imipramine, dothiepin and doxepin), host (\(\beta\text{-CD}\)) and inclusion complexes. From Fig. 2, it can be seen that the guest molecules indeed form stable inclusion complexes with \(\beta\text{-CD}\). Interestingly, it can also be seen that the structures of the above four drug \(\beta\text{-CD}\) inclusion complexes are very similar to each other. Presumably, the fact that the four guest molecules are isoelectronic causes the above behavior. The structural similarity is a likely factor that makes the complexation energies of \(\beta\text{-CD}\) with the four guest molecules same.
From Table 1, it is found that, (i) chemical potential of imipramine is higher than imipramine, dothiepin and doxepin, (ii) the hardness of imipramine and doxepin is higher than imipramine and dothiepin, (iii) electrophilicity of carbamazepine is higher than imipramine, dothiepin and doxepin, (iv) the stability of the complexes are same, (v) doxepin HOMO is more negative than other three drugs, (vi) the HOMO-LUMO gap for imipramine inclusion complex is more negative than other complexes, and, (vii) for all the drug molecules energy, enthalpy, entropy and free energy values are positive.

The \( (E_{\text{HOMO}} - E_{\text{LUMO}}) \) gap is an important scale of stability\(^3\) and chemicals with large \( (E_{\text{HOMO}} - E_{\text{LUMO}}) \) values tend to have higher stability. So, we investigated the electronic structure of the complexes with these considerations using PM3 method. The HOMO–LUMO energy gap of imipramine (-7.63), carbamazepine (-7.13), dothiepin (-7.07) and doxepin (-7.66) were calculated using PM3 and were shown in Table 1 and Fig. 3, which reveal that the energy gap reflected the chemical activity of the molecules. The LUMO as an electron acceptor represents the ability to obtain an electron and HOMO represents the ability to donate electron. Moreover, a lower HOMO–LUMO energy gap explained the eventual stability of the complex, i.e., the isolated molecule had lower stability than the complex molecule. From Table 1, it can be seen that the complexation of \( \beta \)-CD with all the drugs are equal indicating that the stability of the complexes is the same.

The HOMO–LUMO value of the above four inclusion complexes (imipramine (-7.75), carbamazepine (-7.07), dothiepin (-7.92) and doxepin (-7.46)) do not vary significantly; i.e., the energy gap between HOMO and LUMO of each complex suggests that there will be no significant change in the electronic spectrum of the guest molecules driving molecular recognition and binding. This suggests that stability of the above four drug: \( \beta \)-CD inclusion complexes are equal. The similar HOMO of the drugs (Table 1 and Fig. 3) indicates the possibility of similar inclusion complexation processes. However, the HOMO-LUMO gaps for imipramine and doxepin inclusion complexes being more negative suggests that this complex is more stable than the other two drug: \( \beta \)-CD inclusion complexes. The increase of the \( (E_{\text{HOMO}} - E_{\text{LUMO}}) \) gap for the inclusion complexes confirmed the formation of inclusion complexes.

Table 1 shows that the dipole moment of carbamazepine is higher than those of imipramine, dothiepin and doxepin. The dipole moments of dothiepin and doxepin are equal. The dipole moments of the \( \beta \)-CD and the drugs are lower than those of the respective complexes.
(β-CD ~12.29 D, carbamazepine ~2.68 D, imipramine ~2.06 D, dothiepin ~1.41 D, carbamazepine complex ~14.87 D, imipramine complex ~3.25 D dothiepin ~8.76 D and doxepin complex ~9.24 D). The dipole moments of complexes are higher than the dipole moments for resident molecules and lower than that of β-CD (Table 1). This indicates the polarity of the β-CD cavity decreases after the drug enters the cavity. These values demonstrate a strong relationship with the complexation behavior. However, it is not clear why the complexations of β-CD with carbamazepine is more favorable than that with imipramine, dothiepin and doxepin, if the dipole-dipole interaction and hydrophobic interaction are the only driving forces in β-CD complexation.

The results are not readily understandable according to the driving forces, viz., van der Waals force, hydrophobic effect, dipole-dipole and hydrogen bonding interactions. Morokuma theory of energy decomposition analysis offers a reasonable explanation. According to this theory, when a supermolecule is formed, electrons lose their identity as belonging to one or other component molecule. Four types of interactions should be considered in the formation of a supermolecule: (a) electrostatic interaction, which is favored by large permanent charges and dipoles, (b) polarization interaction, which is favored by large volume and polarizability of the molecules, (c) exchange energy, or Pauli repulsion, and, (d) charge-transfer interaction, which is due to the mixing of the filled orbital of one component molecule with the vacant orbital of the other. The charge-transfer interaction is always attractive, and the most important terms in this interaction are contributed from the charge-transfer between the HOMO of one component and the LUMO of the other. These first three interactions constitute the canonical driving forces in CD chemistry, i.e. dipole–dipole interaction, dipole-induced dipole interaction and steric effect. However, these cannot explain the unexpected experimental observations. The higher the HOMO of the guest molecule, the stronger is the charge-transfer interaction in the complexation. Herein, the quantum mechanical studies indicate that there is no charge-transfer present in the interactions of the four drugs with β-CD. Further, Mulliken charge distribution analysis reveals that, the values of the four complexes is zero confirming that there are no charge transfer interactions in the β-CD complexation. Even though β-CD is ready to act as Lewis acid accepting electrons, the guest compounds do not act as Lewis bases donating electrons. Thus, there are no charge

![Fig. 3—The HOMO, LUMO energy structures of (a) carbamazepine, (b) imipramine, (c) dothiepin, and, (d) doxepin. [Blue and yellow colours indicate nitrogen and sulphur atoms respectively whereas the green and red colours indicate negative and positive phase of the molecules respectively].](image-url)
transfer interactions between the HOMO of the drug compounds and the LUMO of β-CD.

Thermodynamics parameters

To investigate the thermodynamics of the inclusion process, the binding energies (ΔE), Gibbs energy changes (ΔG), enthalpy changes (ΔH) and entropy changes (ΔS) for the most stable inclusion complexes (both head-up and head-down configurations) were calculated and are summarized in Table 1. The binding energy (ΔE) of the isolated molecule and complex suggested that stability of complex is high compared to isolated molecule. Even though the energies, enthalpies and entropies of the drugs are positive, the complexation values are negative which demonstrated that the inclusion processes of drugs in β-CD are thermodynamically favorable. The lowest values for complexation energy correspond to the most stable complex. Among the four inclusion complexes, energy of the dothiepin-β-CD inclusion complex is lowest (-195.60 kcal mol⁻¹), followed by imipramine (-15.81 kcal mol⁻¹), then carbamazepine (-10.75 kcal mol⁻¹) and doxepin (-8.24 kcal mol⁻¹). The results indicate that dothiepin formed more stable inclusion complex than the other drugs. The experimental complexation energy varies significantly from the theoretical values¹⁹,²⁰ (dothiepin: Kₜₐₚ ~ 368 mol⁻¹, Kᵢᵤ ~ 569 mol⁻¹; doxepin: Kₜₐₚ ~ 397 mol⁻¹, Kᵢᵤ ~ 624 mol⁻¹; imipramine: Kₜₐₚ ~ 568 mol⁻¹, Kᵢᵤ ~ 763 mol⁻¹ and carbamazepine: Kₜₐₚ ~ 586 mol⁻¹, Kᵢᵤ ~ 780 mol⁻¹).

The ‘ΔE’ values are a reasonable measure of hydrogen bonding and the change in hydrogen bonding of the drugs are caused only by the hydrogen ion concentrations. The energy involved in such hydrogen bond interaction is responsible for the higher/lower binding energy compared to those of the substituted/unsubstituted molecules. The difference in ΔE for these inclusion complexes indicated that the interactions of hydrogen atoms of the guests with β-CD are much stronger than those of the drugs confirming that the interactions are due to the hydrogen bonding. From Table 1 and Fig. 2, marginal variations noticed in ΔE for doxepin: β-CD inclusion complex confirm that hydrophobic interactions have a more significant role in the inclusion complexation process of the doxepin: β-CD complex than in the other complexes¹¹-¹⁵. Figure 2 also suggests that hydrogen bonding are present in carbamazepine and imipramine: β-CD inclusion complexes. In carbamazepine and imipramine, the polar amide and =N– substituents are located near the wider end of the β-CD cavity. From these results, we conclude that the above four drugs are partially included in the β-CD cavity.

The free energy for the isolated drugs are positive whereas negative values are observed in the inclusion complexes. The negative free energy change values (ΔG) of the inclusion complexes suggest that the inclusion proceeded spontaneously at 303 K. The experimental ΔG values (in kcal mol⁻¹): carbamazepine: ΔGₜₐₚ ~ -16.05, ΔGᵢᵤ ~ -16.77; imipramine: ΔGₜₐₚ ~ -15.97, ΔGᵢᵤ ~ -16.72; dothiepin: ΔGₜₐₚ ~ -14.89, ΔGᵢᵤ ~ -15.97; doxepin: ΔGₜₐₚ ~ -15.06, λᵢᵤ ~ -16.22) are different from theoretical values (carbamazepine: ΔGₜₐₚ ~ -20.31; imipramine: ΔGₜₐₚ ~ -24.32; dothiepin: ΔGₜₐₚ ~ -63.47; doxepin: ΔGₜₐₚ ~ -19.57). The high negative ΔG value for dothiepin: β-CD inclusion complex indicates that this inclusion process is more spontaneous than the other complexes.

The difference in ΔE and ΔG can be explained by the solvent effect. The experiments were conducted in aqueous medium and the computational work was done in vacuum phase. We were unable to do the computational work at the aqueous medium due to system limitations. Unfortunately because of limitations in the calculation ability of the computer and the large molecular size of β-CD, calculations for these systems could not be performed for aqueous solutions and excited state. However, it is observed that the solvent effect on the host-guest interactions easily changes the inclusion reaction from a non-spontaneous process in the gas phase to a spontaneous one in the aqueous phase. The host-guest interaction causes an enthalpy-entropy compensating process in the gas phase whereas the same interaction causes an enthalpy-entropy co-driven process in aqueous solution, due to release of number of water molecules from the cavity of β-CD in inclusion complexation.

Recently, some workers who encountered this discrepancy turned to experimental values to adjust their calculations. For example in the case of the complexes of both cis and trans isomers of Brooker’s mercyanine inserted within β-CD cavity, the Hamdi et al.²⁷ calculations of ΔG values predicted that the complex would not form spontaneously and the magnitude and the sign of ΔS and ΔG values were very different from the experiment values. They
argued that since experimentally the entropy of complexation depends on both the insertion of the dye molecule and the concurrent displacement of water molecules that are trapped with in the β-CD cavity, the water molecule should be included in the calculations and then found that the thermodynamic values are closer to the experimental results and the sign matched the reported values in all cases. Further Xing et al. proposed a model to calculate $\Delta S$ of the inclusion complex in aqueous solution with the assumption that the effect of water molecules on the entropy changes of the 2-hydroxy-5-methoxyacetophenone:β-CD system is mainly determined by the water molecules in the β-CD cavity and the effect of the $H_2O$ molecules out of the cavity is less important and thus can be neglected.

Like the free energies, the enthalpies of the isolated drugs are positive whereas the inclusion complexes enthalpies are negative. The negative $\Delta H$ values indicate that the formation of inclusion complexes of the drugs are exothermic and mostly enthalpy-driven ($\Delta H > \Delta S$). It should be noted that $\Delta H$ and $\Delta S$ values contain contributions from (i) release of water found in the β-CD cavity, (ii) partial destruction of hydration shells of the reagents, (iii) non-covalent interactions (van der Waals, hydrophobic and electrostatic interactions as well as hydrogen bonding, and, (iv) hydration of the complexes. All these process should be taken into account while discussing thermodynamic parameters of complex formation.

Dothiepin is bound to β-CD with more negative $\Delta H$ than the other drug complexes. Probably geometric factors play a considerable role in the complexation process. The small positive $\Delta S$ is a confirmation of restriction of freedom of the molecule and formation of less compact structures. As it is evident from Table 1, hydroxyl groups reduce binding affinity of β-CD to drugs, making the complexation process more enthalpy and less entropy favourable. It is assumed that the β-CD cavity size and drugs substituents serve as a steric hindrance for the drug inclusion.

The observed small positive $\Delta S$ values are assumed to be due to enhancement of disorder in the system. Moreover hydrophobic interactions, which are long range interactions, can be important in the β-CD complex formation. The inclusion complex structure in Fig. 2 also suggests that benzene ring was partially inside the cavity and interacts with it through hydrophobic interactions. Further the small $\Delta H$ values can be explained by the presence of hydrophobic interactions. The $\Delta G$ and $\Delta H$ values for the four drugs with β-CD confirm that all the four inclusion complexes are stable. Comparison of $\Delta H$ and $\Delta S$ showed that enthalpy changes are higher and entropy changes are lower for the complexation. Therefore, complexes of the drugs with β-CD are more enthalpy stabilized.

The optimized inclusion structure in Fig. 2 shows formation of hydrogen bond in the imipramine and carbamazepine inclusion complexes whereas in the dothiepin and doxepin inclusion complexes, hydrophobic and electrostatic interactions play a major role. The intermolecular hydrogen bonds are formed between hydrogen atom of hydroxyl group of the β-CD with a $d_{H-O}$ distance less than 3.00 Å and between hydrogen atom of imine group and –OH group of β-CD with a distance of 2.88 Å. This shows that both hydrophobic and electrostatic interaction energies are necessary between the drugs and β-CD to ensure a better inclusion of the guest to the host. The above values are supported by the fact that the flexibility of the host molecule may be one of the structural requirements for inclusion complexes formation. Though the above four drugs have similar volumes, polarizability and hydrophobicity, β-CD complexation with the former two (carbamazepine and imipramine) is stronger than that with latter two (dothiepin and doxepin). However, the present calculation shows that hydrogen bonding is not responsible for the difference between the binding energies of β-CD complexation with carbamazepine, imipramine, dothiepin and doxepin.

The bond distances, bond angles and the most interesting, dihedral angles, of the drugs before and after complexation in β-CD obtained from PM3 calculations for the most stable structure (Fig. 2) are presented in Table 2. It is evident that in β-CD the geometry of the drugs are slightly altered. The alterations are significant in dihedral angles, which indicates that the drugs must adopt a specific conformation to form a stable complex. The internal diameter of β-CD is approximately 6.5 Å and the height is 7.8 Å. Considering the shape and dimensions of β-CD, the four drugs can not be completely embedded in the β-CD nano cavity. The vertical distance and length of the drugs are greater than the upper/lower rim of β-CD. Hence, the aromatic rings can not be fully present inside the β-CD nano cavity.
Therefore, the guest is partially embedded in the phenyl moiety may achieve a maximum contact area and free drugs increased when the hydrophobic guest

Further, the optimized theoretical structure of drugs: β-CD inclusion complex by Gauss view method also confirms that the drugs are partially included in the β-CD nano cavity.

To the best of our knowledge, the thermodynamic parameters (\(\Delta G\), \(\Delta H\), \(\Delta S\)) that describe the 1:1 drug β-CD complexation process are not characterized experimentally so we could not adjust our calculations. Further, from the semiempirical study we noticed that the dipole moment values of β-CD and free drugs increased when the hydrophobic guest entered into the β-CD cavity forming the complex, which is an indication of the increase of the polarity.

It is well known that the van der Waals forces including the dipole–induced dipole interactions are proportional to the distance between guest, the wall of the β-CD cavity and the polarizabilities of the two components. The interaction of the phenyl ring with β-CD may play an important role because the phenyl moiety may achieve a maximum contact area with the internal surface of the cavity of the CD. Therefore, the guest is partially embedded in the β-CD cavity.

The above results suggest that the inclusion of the drug molecules with β-CD nano cavity is affected by hydrophobic and electronic interactions. Since CD has a permanent dipole the primary hydroxyl end is positive and the secondary hydroxyl end is negative in the glucose units of CD. The stability of binding by hydrophobic interaction is partly the result of van der Waals force but is mainly due to the effect of entropy on the water molecules. In the aqueous solution, a hydrophobic guest compound is restricted by the water shell formed by the hydrogen bonding network. It has a strong tendency to break down the water cluster and penetrate the non-polar cavity of the CD. This process is exothermic due to entropic gain. The energy for the inclusion of CD with guest compounds are observed to be proportional to the substituent hydrophobic constant of the guest.

Conclusions

The above study shows that β-CD partially encapsulates the four drug molecules and the stability of the four inclusion complexes is same. The enthalpies of the inclusion complexes indicate that the formation of these complexes are weak exothermic processes, while the negative values for the Gibbs energy changes indicate that the formations of all the complexes are spontaneous processes. The entropy effects for formation of the inclusion complexes are slightly more positive than Gibbs energy and the heat effect. Finally, the computational results indicate that the formation of all the inclusion complexes are enthalpy driven process.

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