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Theoretical Study of the  $\alpha$ -Cyclodextrin Dimer

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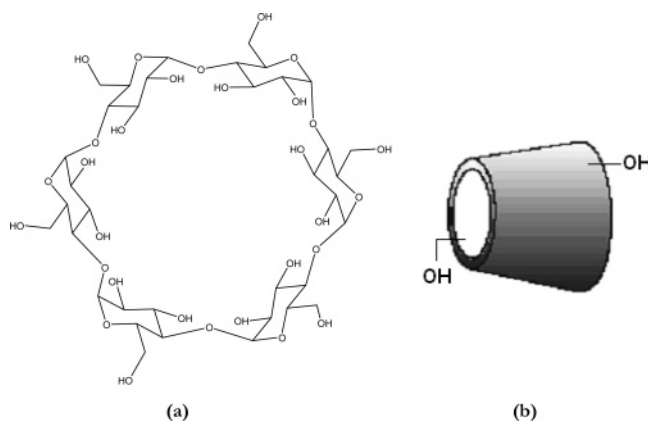
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The molecular structure, stabilization energy, and thermodynamic properties of the plausible modes of the interaction for the three possible  $\alpha$ -cyclodextrin ( $\alpha$ -CD) dimers (head-to-head, tail-to-tail, and head-to-tail) with a water cluster were obtained using quantum chemical methods for the first time. Nine distinct spatial arrangements were investigated. The head-to-head mode of interaction with water is preferred by more than 10 kcal·mol<sup>-1</sup> (BLYP/6-31G(d,p)//PM3 Gibbs free energy difference value at room temperature) in relation to the next stable structure, with a water dimer structure placed inside each cavity and cyclic water tetramers surrounding each tail end. The inter  $\alpha$ -CD hydrogen bonds play a major role to stabilize the dimeric structures, with no water tetramer being found between the two  $\alpha$ -CD subunits for the preferred global minimum structure. Therefore, a theoretical model aimed to describe the behavior of  $\alpha$ -CD dimer, or their inclusion complexes, in the aqueous media should take into account this preference for binding of the water molecules.

## Introduction

The naturally occurring  $\alpha$ -cyclodextrin ( $\alpha$ -CD) is a six-member  $\alpha$ -1,4-linked cyclic oligomers of D-glucose (Figure 1a) and is generally described as a shallow truncated cone (Figure 1b).<sup>1,2</sup> The chemical structure of these molecules presents a hydrophobic cavity due to the presence of hydrogen atoms and ether oxygen's toward the inside of the cavity. In particular, in biochemistry and drug research, the most common cyclodextrins,  $\alpha$ -CD,  $\beta$ -CD, and  $\gamma$ -CD, find important applications because of their multifunctional characteristics and bioadaptability. Recent works show the importance of  $\alpha$ -CD forming inclusion compounds which can act as carriers for biological active substances.<sup>3–8</sup> The principal advantages of natural CD's as drug carriers are (1) a well-defined chemical structure, yielding many potential sites for chemical modification, (2) the availability of CD's of different cavity sizes, (3) low toxicity and low pharmacological activity, and (4) the protection of the included molecule from biodegradation.<sup>9–11</sup>

The driving force responsible to formation of inclusion complexes is the sum of weak secondary interactions for which the thermodynamic parameters are often not readily interpreted. The principal factors involved in the stability of these noncovalent host–guest inclusion complexes are believed to be primarily hydrophobic and van der Waals interactions,<sup>12</sup> although hydrogen bonds are also important to the stabilization of this kind of compounds.<sup>12,13</sup> An inclusion compound can be obtained by techniques that depend on the substrate structure, equilibrium and kinetics properties and the final dosage form desired. Furthermore, each of these aspects depends on the medium properties to help drive the thermodynamics. Usually



**Figure 1.** (a) General structure of  $\alpha$ -cyclodextrin ( $\alpha$ -CD). (b) Topography representation of  $\alpha$ -CD.

the inclusion processes involving CD's are carried out in aqueous solution, then a detailed understanding of the numerous possible structures of water aggregates and their stability is important for obtaining insight into the nature of these inter–water interactions in diverse environments.<sup>14</sup>

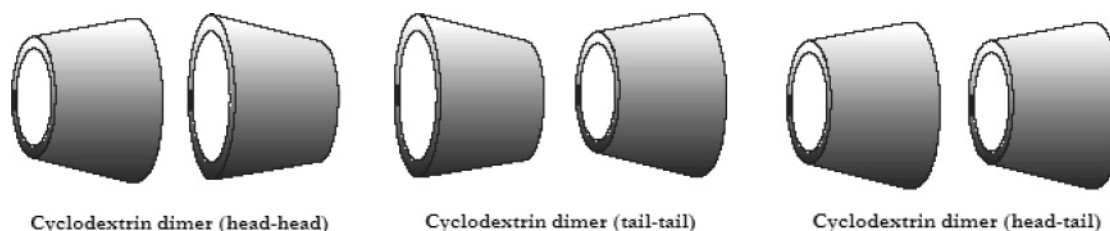
The moderate size of the hydrophobic molecular cavity of  $\alpha$ -CD prevents the accommodation of large substrates by only one cyclodextrin. However, a variety of singly linked CD dimers have been constructed over the years and efficient binding of large substrates can be achieved in 2:1 or 2:2 host:guest inclusion compounds.<sup>15–20</sup> The formation of aggregates in aqueous solution of pure CD's has also been experimentally detected.<sup>21–22</sup>

In recent works, Jaime et al.<sup>23,24</sup> have investigated the three possible orientations between CD's units, i.e., the head-to-head (HH), tail-to-tail (TT), and head-to-tail (HT) structures (Figure 2), using molecular mechanics (MM) and molecular dynamics

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**Figure 2.** Three orientations for the cyclodextrin dimers, named HH (head-to-head), TT (tail-to-tail) and HT (head-to-tail), respectively.

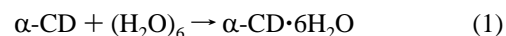
(MD) simulation. The results concerning the first study in a vacuum<sup>23</sup> point toward the HH orientation as the most stable for the three native CD's studied. However, when the authors considered, in the second study,<sup>24</sup> the solvent effect, a different behavior was found for the same CD's dimers, where the HT isomer was more favorable for  $\alpha$ -CD and the TT structure preferred for  $\beta$ - and  $\gamma$ -CD dimers. The HT geometry for the  $\alpha$ -CD dimer adopts a perpendicular arrangement.<sup>24</sup> Obviously, solute–solvent interactions are responsible for these differences and also for the conformational changes observed on the CD's dimer structures. The dimerization process of  $\beta$ -CD was investigated in gas phase by Avakyan and co-workers<sup>25</sup> at the PM3 level. The authors concluded that the HT dimer is energetically more favorable than the HH. This was attributed to the geometric factors and to the higher proton affinity of the primary OH groups, which act as proton acceptors.

In a very recent paper,<sup>26</sup> we addressed the problem of the hydration of  $\alpha$ -CD, using a quantum chemical approach, where we showed that the explicit consideration of the interaction with water clusters produced a very good agreement with experimental thermodynamic data (enthalpy and entropy of hydration). There have been many theoretical studies addressing the structure and energetic of water clusters, especially Monte Carlo and molecular dynamics simulations, with the quantum simulations using the rigid body diffusion Monte Carlo method from ref 27 being a representative example. Some reviews on this subject can be found in refs 28–32. Quantum chemical calculations for isolated water clusters predict ringlike structures, which are also supported by the simulation results. However, it is opportune to mention that at critical conditions ( $T = 647$  K,  $p = 22.1$  MPa) linear clusters are preferred,<sup>33</sup> showing the importance of the pressure and temperature effects on the structure of liquid water. Very recently the structure of liquid water was investigated on the subfemtosecond time scale by X-ray absorption spectroscopy<sup>34</sup> and the results predicted structures with two strong hydrogen bonds (one donor and one acceptor bond) of each molecule to its neighbors, resulting in water chains and rings. Therefore, any theoretical attempt to describe the interactions of cyclodextrins in water should include the temperature and pressure effects through the calculation of enthalpic and entropic contributions and a description of the hydrogen bond interactions using a quantum mechanical treatment. We have shown in ref 26 that the evaluation of the thermal correction at a quantum chemical semiempirical level (PM3) and the electronic plus nuclear repulsion energy at the density functional theory (DFT) level of theory provides a good agreement with the experimental data for the hydration of the  $\alpha$ -CD. We therefore believe that such procedure should also be used to treat the  $\alpha$ -CD dimer in water. It is well-known that the evaluation of the entropy contribution through simulation methods is not an easy computational task, but it can be calculated at an affordable computational cost using a semiempirical method. This proposal for calculating the thermodynamic properties of large molecules and interacting systems, where H-bonds play a role, was first proposed by us in ref 26.

In the present work, we investigated the formation of the  $\alpha$ -cyclodextrin dimers using the PM3 and DFT (BLYP functional) levels of calculation. Our goal is to analyze the interactions between water molecules and  $\alpha$ -CD, based on thermodynamic quantities, and then to predict the preferred structures for the  $\alpha$ -CD dimer in aqueous media. The understanding of the interaction of  $\alpha$ -CD dimer with water at a molecular level is very relevant, since the hydrogen bonding which plays an important role must be described using an adequate treatment of electron correlation that can be satisfactorily achieved by DFT methods, as far as H-bonded complexes are concerned. In addition, our results can be relevant to the areas of supramolecular chemistry and nanoscience.

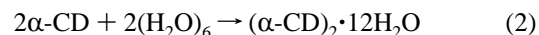
### Computational Methodology

In our previous paper,<sup>26</sup> the thermodynamics properties of the hydration of  $\alpha$ -cyclodextrin ( $\alpha$ -CD) was computed and compared with the experimental data. Two distinct chemical equations were considered with the better agreement found for process 1.



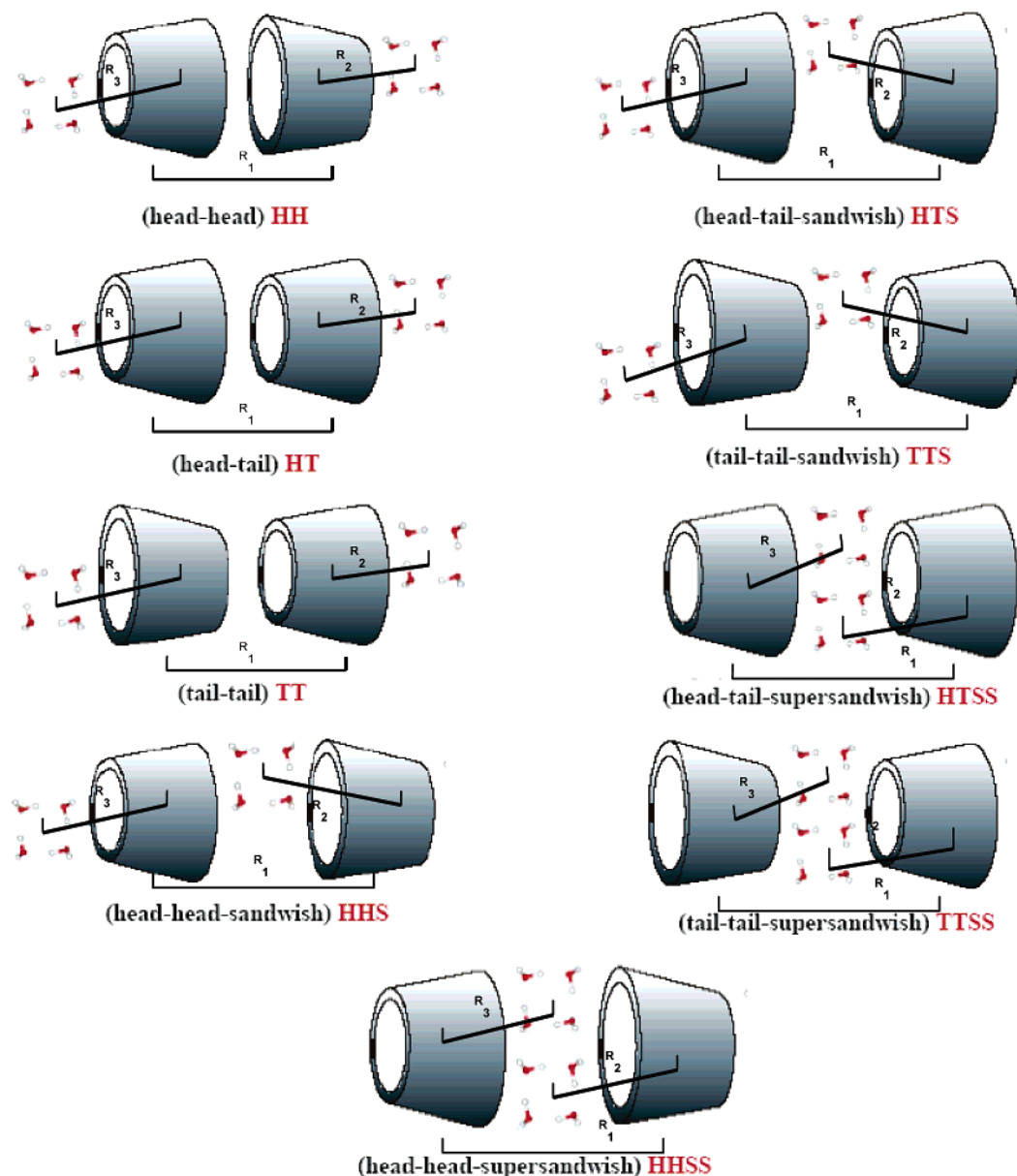
The  $\alpha\text{-CD}\cdot 6\text{H}_2\text{O}$  species contains the water dimer inside the cavity and a tetramer outside, situated either on the wider rim (*down* structure) or smaller rim (*up* structure). The  $\Delta G$  in gas phase at the BLYP/6-31G(d,p)/PM3 level were  $-4.0$  (*down*) and  $-1.8$  kcal·mol<sup>-1</sup> (*up*).

In the present work, the dimerization of  $\alpha$ -CD was considered and the thermodynamic properties calculated according to process 2.



In this proposal, we have considered the interaction between two cyclic well-known water hexamers and two  $\alpha$ -CD monomers. Furthermore, we assumed that two water molecules are situated inside the cavity of each  $\alpha$ -CD, and two water tetramers surrounding it below or above the cavity, somehow similar to the  $\alpha$ -CD *down* (larger cavity) or *up* (smaller cavity) preferred structures for the hexahydrate species found in our previous work.<sup>26</sup> We can also rewrite the right side of eq 2 as a complex of  $\alpha$ -CD dimer, a  $\text{H}_2\text{O}$  dimer inside the cavity of each CD and two water tetramers outside, i.e.,  $[(\alpha\text{-CD})_2\cdot 2(\text{H}_2\text{O})_2]\cdot 2(\text{H}_2\text{O})_4$ . So, nine distinct spatial arrangements were obtained. The schematic representation of the possible structures for the  $\alpha$ -CD dimer dodecahydrate is represented in Figure 3.

The geometries of the water hexamer,  $\alpha$ -CD and the nine plausible hydrated forms, having the water tetramers at the larger (*down*) or smaller (*up*) cavity, with a water dimer placed inside the cavity of each CD, were fully optimized without any geometrical or symmetry constraints using the semiempirical PM3 method,<sup>35</sup> which has been shown to give very reasonable geometrical parameters for cyclodextrins.<sup>25,36</sup> PM3 harmonic frequency calculations were performed for the equilibrium



**Figure 3.** Nine possible  $\alpha$ -CD dimer dodecahydrate structures. The S and SS labels stand for sandwich and super-sandwich interaction modes, respectively. There is a water dimer structure inside each  $\alpha$ -CD cone, not shown in this picture for reason for simplicity. Some relevant center of mass distances are indicated:  $R_1$  is the dimer center of mass distance;  $R_2$  and  $R_3$  are the distances between a water tetramer and the center of mass of a  $\alpha$ -CD monomer;  $R_4$  and  $R_5$  are respectively the distances between the center of mass of a water dimer placed inside the cavity of the  $\alpha$ -CD monomer and its respective center of mass (not shown).

structures, characterizing them as true minima on the potential energy surface. The PM3 frequencies were then used for the evaluation of the internal energy ( $\Delta E_{\text{int}}$ ) and thermal energy ( $\Delta G_T$ ) corrections, with the aid of the well-known formulas of statistical thermodynamics.<sup>37</sup> We calculate the enthalpy ( $\Delta H$ ) and Gibbs free energy ( $\Delta G$ ) of process 2 using the equations below, a procedure that was successfully used in refs 26 and 38.

$$\Delta H = \Delta E_{\text{ele-nuc}} + \Delta E_{\{\text{int}\}} \quad (3)$$

$$\Delta G = \Delta E_{\text{ele-nuc}} + \Delta G_T, \text{ where } \Delta G_T = \Delta E_{\{\text{int}\}} - T\Delta S \quad (4)$$

The  $\Delta E_{\text{int}}$  (eq 3) is the contribution from the internal thermal energy plus  $RT$ , which strictly means the enthalpy change of the process without electronic plus nuclear repulsion energy. The  $\Delta S$  (eq 4) is the entropy change calculated from the electronic, translational, rotational and vibrational partition

functions.<sup>37</sup> The electronic plus nuclear repulsion contribution ( $\Delta E_{\text{ele-nuc}}$ ) to  $\Delta H$  and  $\Delta G$  were evaluated at the density functional theory (DFT) level using the gradient generalized BLYP functional<sup>39,40</sup> at the fully optimized PM3 geometries, with the Pople's standard split valence 6-31G(d,p) basis-set<sup>41</sup> containing polarization functions on all atoms (BLYP/6-31G(d,p)/PM3). The  $\Delta E_{\text{int}}$  and  $T\Delta S$  terms were evaluated with the PM3 geometrical parameters and harmonic frequencies, which have been shown to yield a good agreement with the experimental thermodynamic data for  $\alpha$ -CD.<sup>26</sup>

All calculations were carried out at the Laboratório de Química Computacional e Modelagem Molecular (LQC-MM), Departamento de Química, ICEx, UFMG, using the Gaussian-98 quantum mechanical package.<sup>42</sup>

## Results and Discussion

It is clear that the water effect on the interaction between two CD's might be very important due to the tendency of the

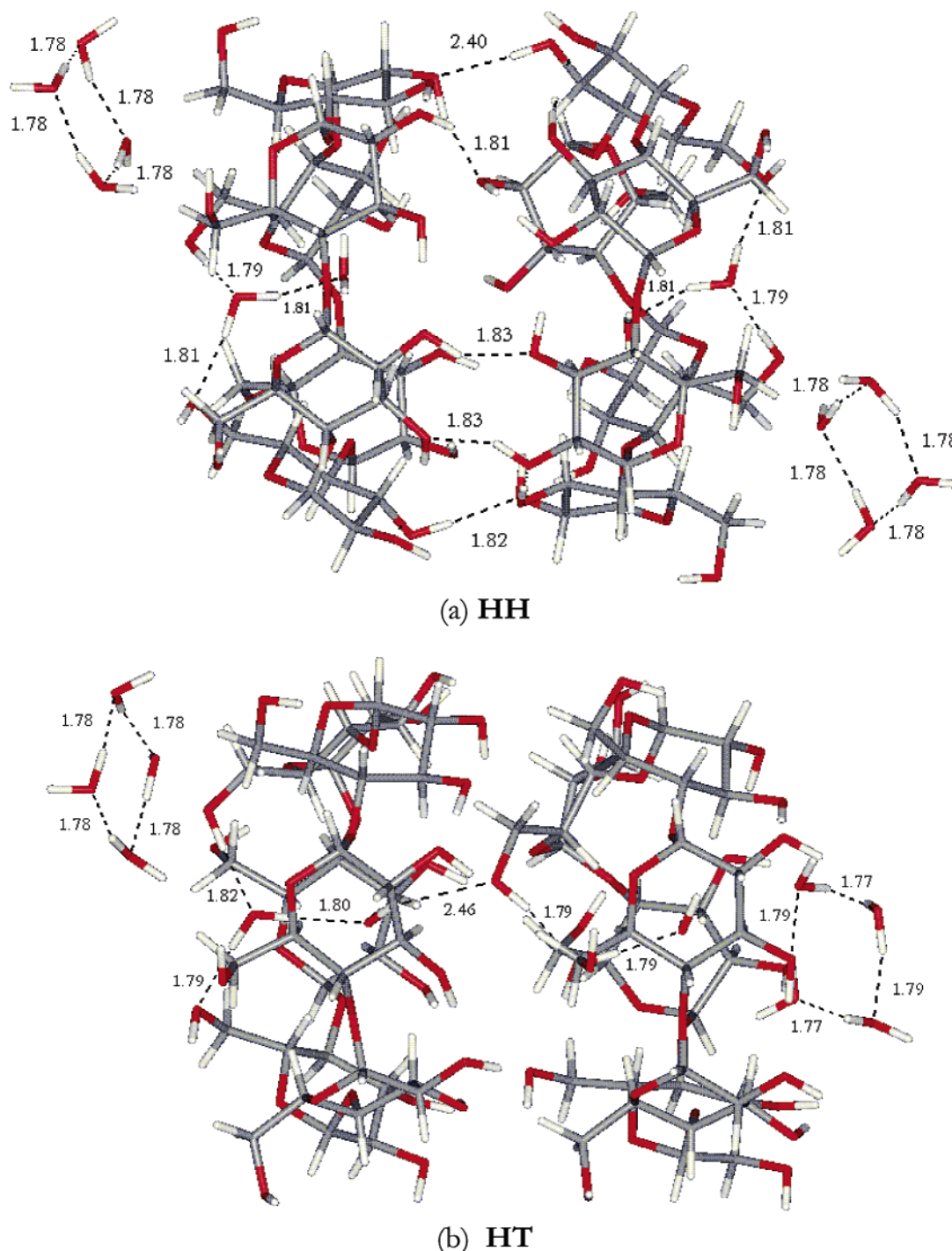


Figure 4.

CD's to approach each other as the result of the formation of several intermolecular hydrogen bonds. Then, if the hydrogen bonds between the hydroxyl groups of CD's are the major driving force for holding the two units together, their interaction with water molecules will compete with the intermolecular CD $\cdots$ CD hydrogen bonds, and the stability of the dimers will be changed.

First, a detailed structural analysis of the nine possible  $\alpha$ -CD dimer dodecahydrate was carried out, aiming to evaluate the trend in the PM3 semiempirical geometries for these compounds. The respective optimized structures are depicted in Figure 4, with some relevant intermolecular distances being also quoted. Analyzing the obtained structures, we observe that the  $\alpha$ -CD structures do not change much on dimerization, a result that

may be an evidence of the high computational efficiency of PM3 Hamiltonian on structural description of large systems.<sup>43,44</sup> Furthermore, our previous structural study on cyclodextrins provides support for the capacity of the PM3 method.<sup>36</sup> The structural analysis shows that hydrogen bonds between the two CD's units forming the dimer and between each CD with the water tetramers play a fundamental role to stabilize the dimeric structure, with no water tetramer being found between the two  $\alpha$ -CD subunits as the preferred structural arrangement. BLYP/6-31G(d,p)/PM3 calculations indicated that the formation of the HH orientation was the most energetically favored. For this configuration, five hydrogen bonds were identified when it was considered as a hydrogen bond O $\cdots$ O distances shorter than 2.5 Å. The existence of several glucoses turned over for each



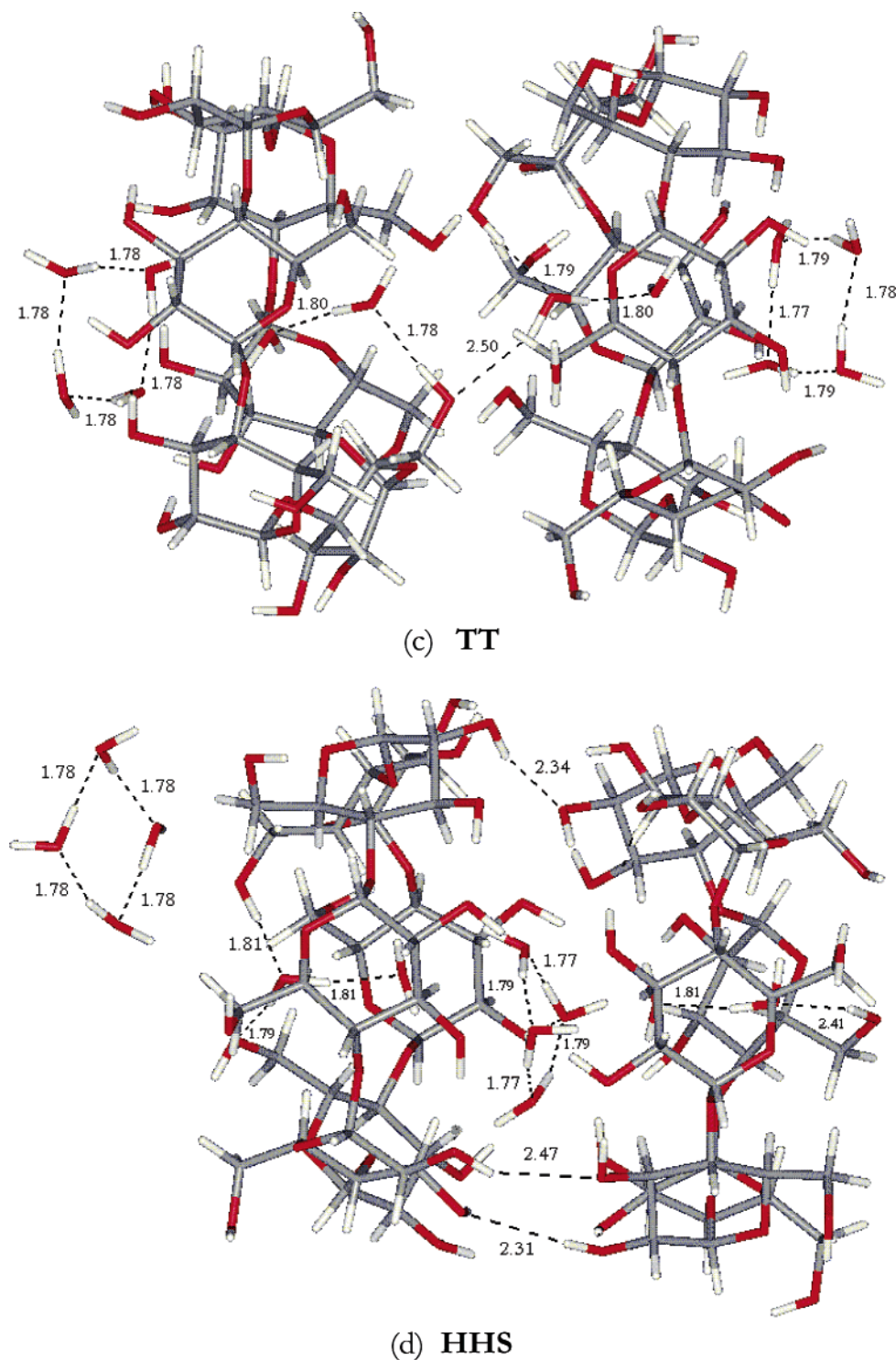


Figure 4. Continued

$\alpha$ -CD and the absence of water cluster between the two CD's permits the formation of these intermolecular hydrogen bonds. For the  $\beta$ -CD the theoretical (PM3) predicted average intermolecular O...O distance on the HH isomer was  $\sim 3.3$  Å, larger than the values found in this work. It might be associated with the low stability of the HH dimer for  $\beta$ -CD.<sup>25</sup>

Table 1 contains relevant intermolecular center of mass distances involving the  $\alpha$ -CD monomer, water dimer, and tetramer, and Table 2 gives the molecular interaction energy in the perfect vacuum ( $\Delta E_{\text{ele-nuc}}$ ) and thermodynamic properties for the dimerization process of  $\alpha$ -CD for the temperature and pressure conditions of 298.15 K and 1 atm, respectively. From

Figure 3 and Table 1 it can be seen that the dimer center of mass (CM) distance ( $R_1$ ) has its smallest value for the global minimum HH structure, with the distance between the  $\alpha$ -CD monomer and water tetramer CM ( $R_2$  and  $R_3$ ) having essentially the same value, so an approximately symmetric spatial configuration is obtained (Figure 4a). From the fifth and sixth columns of Table 1 it can be seen that the CM of the water dimer placed inside the  $\alpha$ -CD cavity is very near to the respective CM of each  $\alpha$ -CD subunit ( $R_4$  and  $R_5 < 1.2$  Å), due to the fact that the water dimer is almost occupying the center of the cavity. Therefore, all structural considerations can be made assuming that each  $\alpha$ -CD monomer has a water dimer built in its CM,

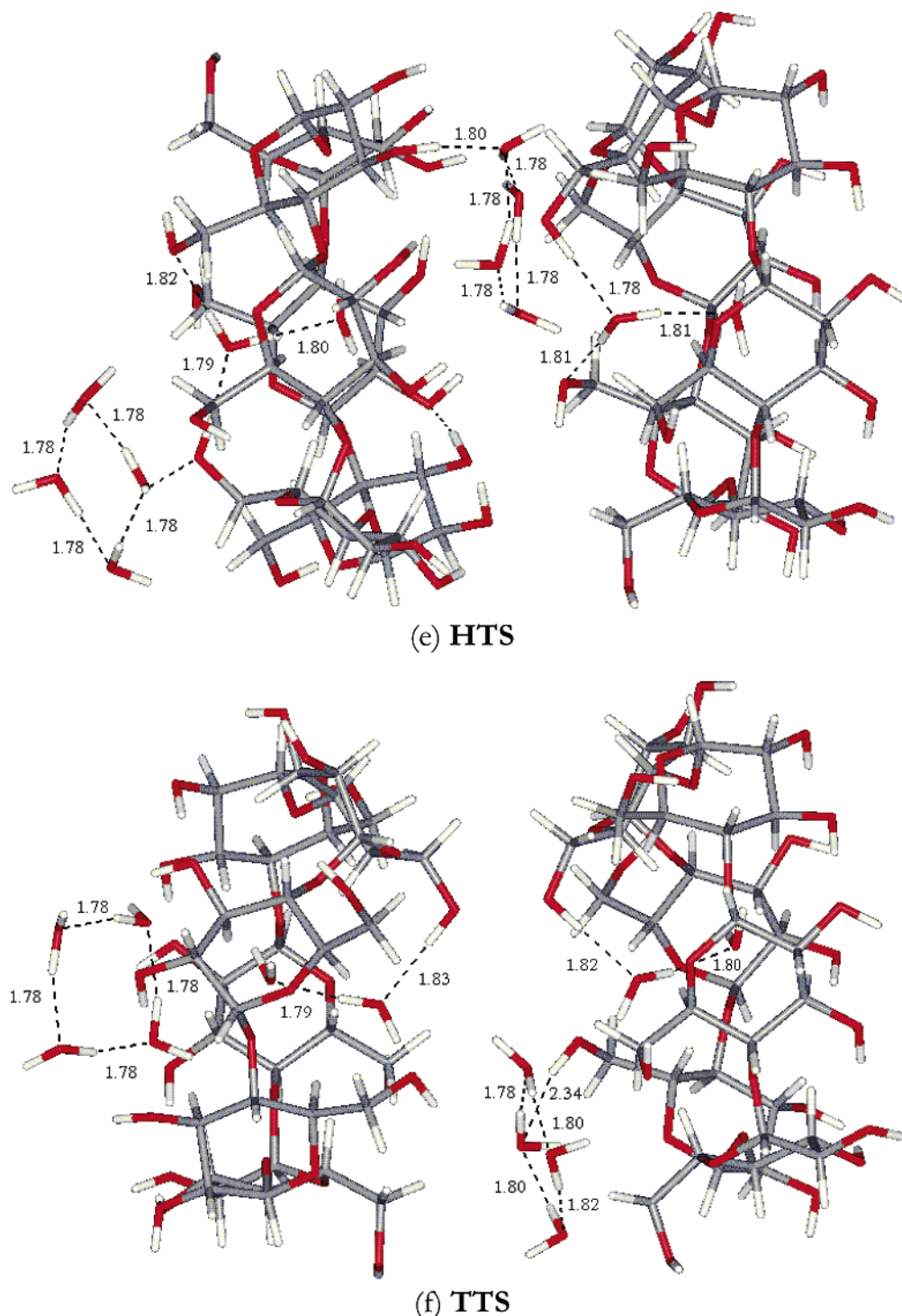


Figure 4. Continued

and so we need to consider explicitly only the  $R_1$ ,  $R_2$ , and  $R_3$  CM distances. For the super-sandwich (SS) dimers, having two water tetramers trapped between two  $\alpha$ -CD monomers, the CM distance between the two tetramers is given in parentheses of Table 1. This distance correlates with the opposite stability order of the HHSS, HTSS, and TTSS dimers. The shortest intermolecular CM distance between tetramers occurs for the TTSS dimer, so making an attractive contribution for its still small Gibbs free energy complexation value of  $-0.21 \text{ kcal}\cdot\text{mol}^{-1}$ . It can be seen that what makes this structural arrangement tightly bound is the attractive interaction between the two water tetramers trapped between the two  $\alpha$ -CD monomers. In the absence of the  $\alpha$ -CD monomers the tetramer interaction would

lead to the formation of a water octamer stable structure. The energetic features of the gas-phase process  $2\text{T} \rightarrow \text{O}$ , where T and O stand for a water tetramer and octamer ( $D_{2d}$  symmetry), respectively, have been evaluated,<sup>46</sup> and the reported values for the enthalpy and Gibbs free energy are respectively  $-12.86$  and  $1.84 \text{ kcal}\cdot\text{mol}^{-1}$  (MP2//HF value using a Dunning's double- $\zeta$  polarized basis set). This  $\Delta G$  of reaction value is the lowest in the series dimer, trimer and tetramer, reported in ref 46, so, in agreement with our predictions that the closeness of two water tetramer may increase the stabilization of the TT and HT dimers as shown in Tables 1 and 2. It is worthwhile to say that the ab initio CM distance between two tetramers reported in ref 46 would be approximately  $3 \text{ \AA}$ , while our shortest tetramer–

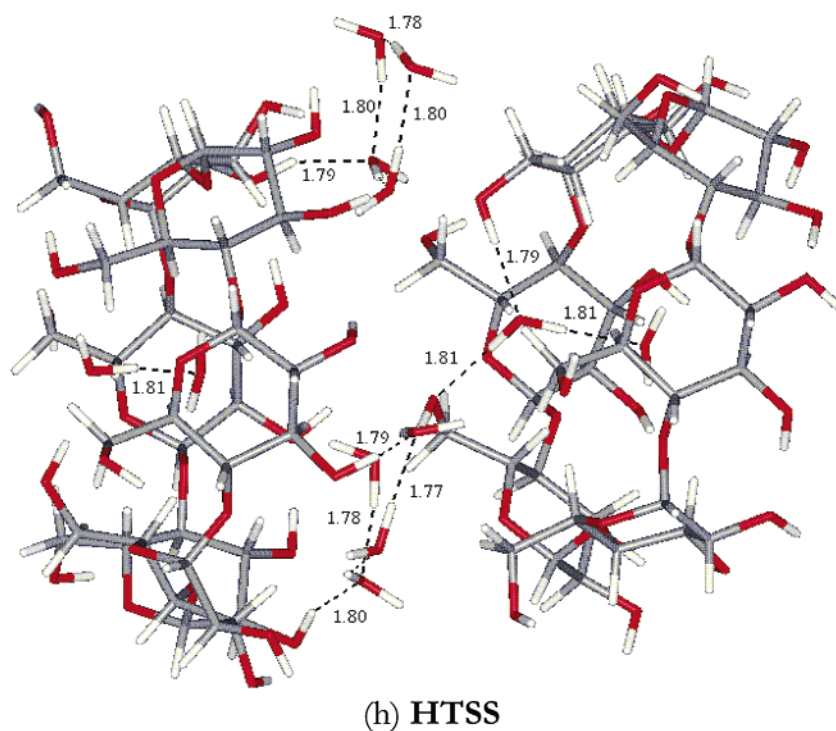
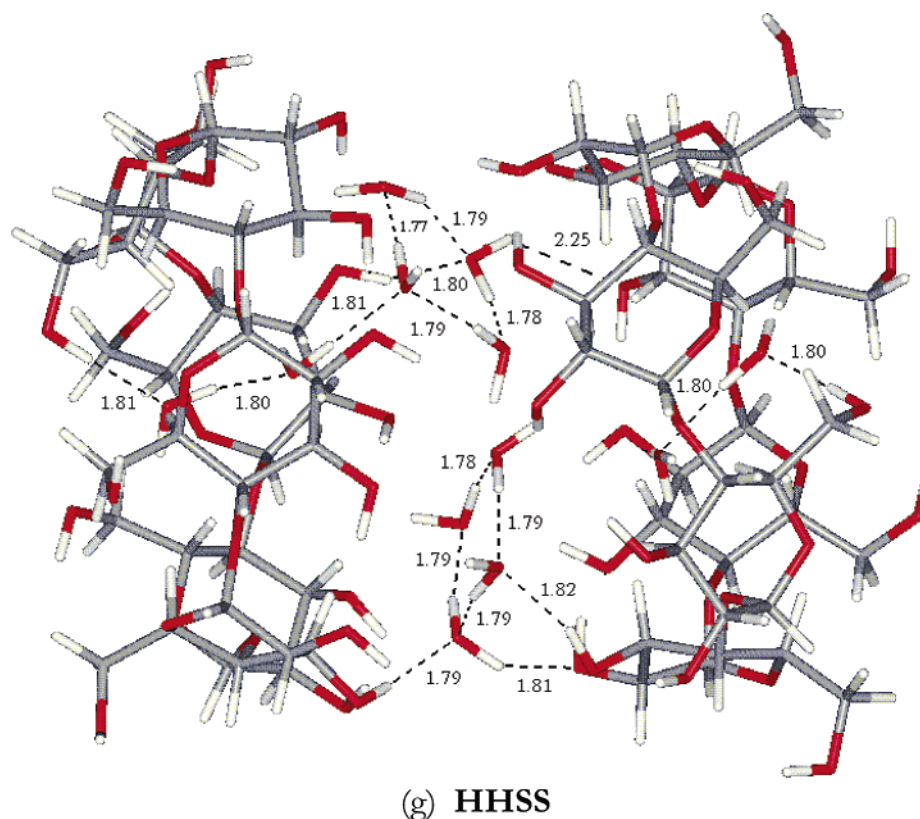


Figure 4. Continued

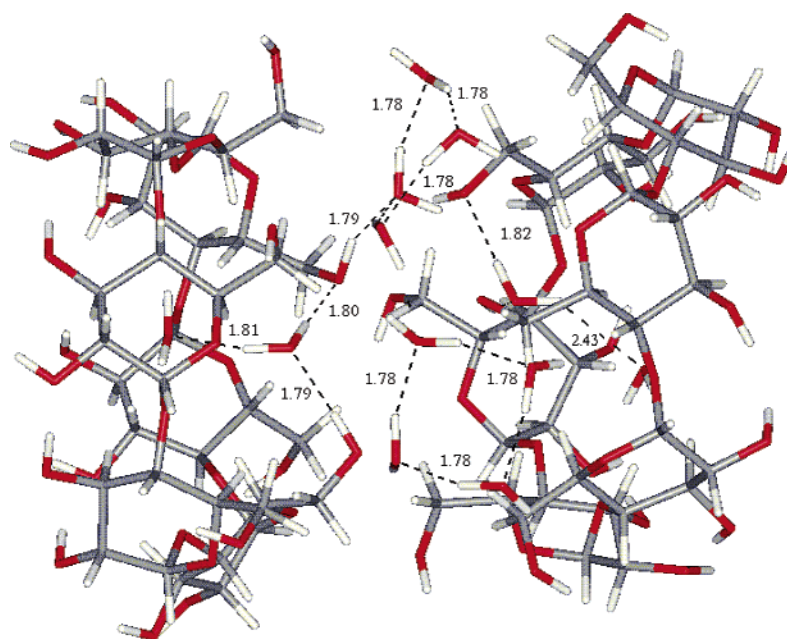
tetramer CM distance here is 6.61 Å, for the TTSS structure, thus being almost twice the distance apart from each other than that in the isolated water octamer structure reported in ref 46.

In the last row of Tables 1 and 2, we report our results for the perpendicular-like structure of the HT dimer proposed in the molecular dynamics study reported in ref 24. The fully optimized structure is also shown in Figure 4j. It can be seen that the perpendicular structure is indeed not favorable at the BLYP/6-31G(d,p)/PM3 level of calculations, which strength

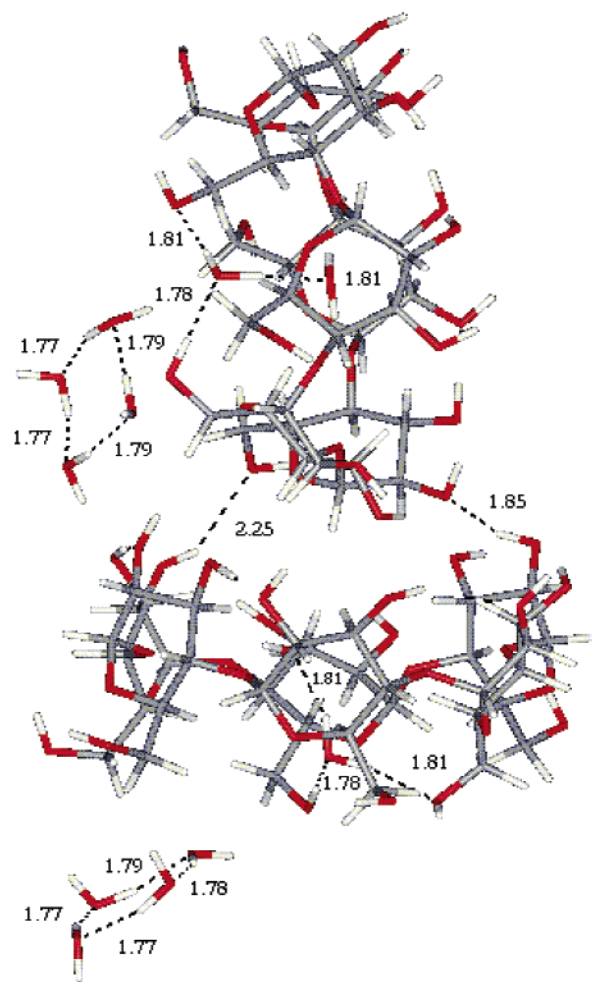
our predictions regarding the preference for the HH configuration.

Analyzing the results of Table 1, it can be seen that the inclusion of water tetramers between the two  $\alpha$ -CD monomers, increases the  $R_1$  distance considerably for all dimers, as would be expected, however, having a distinct effect on the  $\Delta G$  values (see Table 2) destabilizing the HH dimer and stabilizing the HT and TT dimers. The inclusion of water tetramer trapped between the two  $\alpha$ -CD subunits drops the relative stability of





(i) TTSS



(j) HT-perpendicular

**Figure 4.** PM3 fully optimized structures for the nine possible spatial arrangements of the  $\alpha$ -CD dimer dodecahydrate. The S and SS labels stand for sandwich and super-sandwich interaction modes respectively, i.e., one and two water tetramers intercalated. Key: (a) HH; (b) HT; (c) TT; (d) HHS; (e) HTS; (f) TTS; (g) HHSS; (h) HTSS; (i) TTSS (j) HT-perpendicular (PM3 fully optimized perpendicular-like structure proposed in ref 24).

**TABLE 1: Intermolecular Center of Mass (CM) Distances ( $R_i$  in Angstrom) between the Two  $\alpha$ -CD Monomers, Water Dimer and Water Tetramer, as Defined in Figure 3, and the Gibbs Free Energy Values Calculated with the PM3 Fully Optimized Geometry ( $\Delta G^{\text{BLYP/6-31G(d,p)}}$  in kcal·mol<sup>-1</sup>)**

$\alpha$ -CD dimer	$R_1$	$R_2$	$R_3$	$R_4$	$R_5$	$\Delta G$
HH	7.360	7.194	7.189	1.161	0.979	-27.02
HHS	7.633	7.122	4.039	0.925	0.118	-14.38
HHSS	9.206	5.547 (8.582) <sup>a</sup>	6.228	0.331	0.151	-4.45
HT	7.459	4.333	7.078	0.738	1.077	36.77
HTS	9.431	7.028	7.359	1.048	1.042	13.58
HTSS	9.755	5.215 (7.170) <sup>a</sup>	6.801	0.957	0.949	15.50
TT	8.125	3.690	4.189	0.925	0.975	19.64
TTS	9.867	6.329	4.198	0.647	0.962	6.53
TTSS	9.485	6.400 (6.607) <sup>a</sup>	7.564	0.568	1.065	-0.21
HT-perp <sup>b</sup>	9.782	7.136	7.432	0.896	1.184	1.80

<sup>a</sup> Distance between the center of mass of the two water tetramers.<sup>b</sup> Perpendicular like structure as proposed in ref 24.

the isomers HHSS and TTSS to 4.2 kcal·mol<sup>-1</sup>, completely different from the Gibbs free energy difference value of 46.68 kcal·mol<sup>-1</sup> predicted between the TT and HH structures. This shows that if a water tetramer intercalates the two  $\alpha$ -CD monomers it tends to keep them apart so destabilizing the global minimum HH dimeric structure, which also correlates well with the largest monomer-monomer  $R_1$  distance of 9.21 and 9.49 Å respectively for the HHSS ( $\Delta G = -4.45$  kcal·mol<sup>-1</sup>) and TTSS ( $\Delta G = -0.21$  kcal·mol<sup>-1</sup>) structures. So, it can be said that the presence of the water tetramer intercalating the two  $\alpha$ -CD monomers stabilizes considerably the HT and TT structures in relation to the global minimum HH dimer. Therefore, once water molecules can be placed between two  $\alpha$ -CD monomers, the TT mode of interaction starts to play a role in the energetic balance. In addition, the HT type dimer would always play a less important part on the thermodynamic balance. It appears to us that the formation of a  $\alpha$ -CD dimer with water tetramers as intercalating agent, such as the TTSS structure, may be an interesting way of making available two large cavity sides for inclusion complexation with guest molecules doubling the encapsulating power. We may even think about a  $\alpha$ -CD tetrameric structure by adding two  $\alpha$ -CD monomers to each side of the TTSS dimer with water tetramers bound to the smaller cavity as a way to build a nanotube of  $\alpha$ -cyclodextrin, which may even enlarge the encapsulating capacity. Work is already in progress in our laboratory addressing the formation of higher ( $\alpha$ -CD·6H<sub>2</sub>O)<sub>n</sub> clusters.

The enthalpic gain due to the hydrophobic binding of a substrate by a cyclodextrin is partially compensated by the loss of entropy because of the molecular association. For such processes the driving force is the entropy gain due to dewetting of the hydrophobic substrate upon inclusion.<sup>47</sup> This should be less important for the formation of cyclodextrin dimers where the monomer units are hydrophilic species. Then we do not expect great variation on the solvent entropy. The quantification of the solvent entropy change is a quite difficult task and would depend on the (i) desolvation of isolated component ( $\Delta S > 0$ ), (ii) dimerization ( $\Delta S < 0$ ), and (iii) solvation of the dimer ( $\Delta S < 0$ ). In our study only the contribution from step ii was taken into account; steps i and iii depend explicitly on the solvent and cannot be accounted for using static quantum mechanical calculations. It can be seen from Table 2 that the dimer formation process in the presence of water clusters is entropically unfavorable by a sizable amount of ca. 50–55 kcal·mol<sup>-1</sup>

(PM3  $-T\Delta S$  value) with the intermolecular hydrogen bond interaction energy contribution being responsible for the dimer stabilization. It can also be seen from Table 2 that the semiempirical PM3 level of theory is not adequate to describe the H-bond interaction energy in the  $\alpha$ -CD dimer, yielding a too small stabilization energy and consequently a large positive  $\Delta G$  value. Using the DFT method (BLYP functional), which carry at least partially the electronic correlation effects for H-bonded dimers,<sup>48</sup> bound dimer structures ( $\Delta G < 0$ ) are predicted. We here emphasize that we need to use an adequate quantum mechanical method for describing the hydrogen bond interactions in order to reach meaningful Gibbs free energy results which can be compared to the pressure-temperature dependent experimentally observed values. The main contribution to the Gibbs free energy difference comes from the electronic plus nuclear repulsion energy part ( $\Delta E_{\text{ele-nuc}}$ ). The variation goes as higher as 60 kcal·mol<sup>-1</sup> on going from the HH to the HT dimeric structure; while the corresponding variation in the  $T\Delta S$  term is ca. 3 kcal·mol<sup>-1</sup> (the maximum variation found in the thermal energy correction term ( $\Delta G_T$ ) is ca. 6 kcal·mol<sup>-1</sup>). Again our results stress the need of a suitable quantum mechanical approach to study such a process, since the  $\Delta E_{\text{ele-nuc}}$  part plays a major role. Whether or not the BLYP/6-31G(d,p) level of calculation would under or overestimate the interaction energies compared to standard post-Hartree-Fock methods, such as for example MP2 (second-order Møller-perturbation Theory) and CCSD (coupled-cluster with single and double excitations), will not change the conclusions of the present study as long as we can guarantee that the BLYP functional provides a reasonable description of hydrogen bonding. We would like to call the attention here to the behavior of the PM3 approach for describing the thermodynamic properties. The energetic order (and the size of the energy separation) is very different from the BLYP/6-31G(d,p) prediction. It can be seen from the last column of Table 2 that it hardly differentiates between the HH, HHS, and HHSS dimers and also HTS, TTS, and TTSS. Using the PM3  $\Delta E_{\text{ele-nuc}}$  values, the calculated relative Gibbs free energy difference between the HH and HHSS structures is ca. 0.2 kcal·mol<sup>-1</sup>, with the HHS dimer being the global minimum structure. This behavior is quite different from the DFT description, where the HH dimer is predicted to be the global minimum followed by the HHS and HHSS structures by relative  $\Delta G$  difference values of 12.6 and 22.6 kcal·mol<sup>-1</sup>, respectively. In light of these results, it can be concluded that the PM3 approach has no sensitivity to describe the distinct hydrogen bond strengths present in the hydrated  $\alpha$ -CD dimers, yielding a rather almost degenerated structure according to the  $\Delta G$  values reported in the last column of Table 2. However, the semiempirical method can be used for the determination of structural parameters,<sup>25,36</sup> since they are less sensitive to the quantum mechanical level of calculation than the electronic plus nuclear repulsion energy.

It is now important to consider the stability of the dimer analyzing the dissociation process into two hexahydrate monomers, establishing the equilibrium  $2(\alpha\text{-CD}\cdot 6\text{H}_2\text{O}) \rightarrow (\alpha\text{-CD})_2\cdot 12\text{H}_2\text{O}$ . The  $\Delta G_{\text{st}}$  was calculated for this process considering the values of  $\Delta G$  for process 2 (see Table 2) and process 1 ( $\Delta G_1 = -4.0$  kcal·mol<sup>-1</sup> from ref 26) as  $\Delta G_{\text{st}} = \Delta G - 2\Delta G_1$ . The results are reported in parentheses in Table 2. From these data it can be clearly seen that the isomer HH is the most stable one followed by HHS and HHSS. The addition of one water cluster between the CDs in the HH configuration reduces the stabilization free energy ( $\Delta G_{\text{st}}$ ) from -19.0 to -6.40 kcal·mol<sup>-1</sup>, and when two water tetramers are placed between the CDs the

**TABLE 2: Interaction Energy ( $\Delta E_{\text{ele-nuc}}$ ) and Thermodynamic Properties for the Hydration Process of  $\alpha$ -Cyclodextrin Dimer According to the Equation  $2(\alpha\text{-CD}) + 2(\text{H}_2\text{O})_6 \rightarrow (\alpha\text{-CD})_2 \cdot 12\text{H}_2\text{O}$  with Values in  $\text{kcal}\cdot\text{mol}^{-1}$  Calculated at 298.15 K and 1 atm<sup>a</sup>**

	$\Delta E_{\text{ele-nuc}}$		PM3			BLYP <sup>b</sup>		PM3	
	PM3	BLYP <sup>b</sup>	$\Delta E_{\text{int}}$	$T\Delta S$	$\Delta G_{\text{T}}$	$\Delta H^c$	$\Delta G^c$	$\Delta H$	$\Delta G$
HH	-16.52	-81.57	2.37	-52.17	54.55	-79.20	-27.02 (-19.0)	-14.15	37.83
HHS <sup>d</sup>	-19.39	-69.03	1.71	-52.92	54.65	-67.32	-14.38 (-6.40)	-17.68	35.26
HHSS <sup>d</sup>	-21.79	-53.97	4.45	-54.99	59.46	-49.52	-4.45 (3.55)	-17.34	37.67
HT	-10.12	-20.08	1.38	-55.46	56.85	-18.70	36.77 (44.8)	-8.74	46.73
HTS <sup>d</sup>	-10.28	-35.77	1.65	-47.69	49.35	-34.12	13.58 (21.6)	-8.63	39.07
HTSS <sup>d</sup>	-8.92	-44.39	4.47	-55.42	59.89	-39.92	15.50 (23.5)	-4.45	50.97
TT	-16.86	-39.53	2.90	-56.25	59.17	-36.63	19.64 (27.6)	-13.96	42.31
TTS <sup>d</sup>	-18.83	-51.86	3.67	-54.70	58.39	-48.19	6.53 (14.5)	-15.16	39.56
TTSS <sup>d</sup>	-16.94	-53.75	2.76	-50.76	53.54	-50.99	-0.21 (7.79)	-14.18	36.60
HT-perp <sup>e</sup>		-49.91	2.70	-49.02	51.72	-47.21	1.80 (9.80)		

<sup>a</sup> The values in parentheses are stabilization free energies ( $\Delta G_{\text{st}}$ ) calculated as  $\Delta G_{\text{st}} = \Delta G - 2\Delta G_1$ , where  $\Delta G_1$  stands for the Gibbs free energy of process 1 ( $\Delta G_1 = -4.0 \text{ kcal}\cdot\text{mol}^{-1}$ ). <sup>b</sup> The DFT calculations were carried out at BLYP/6-31G(d,p)//PM3 level. <sup>c</sup> The  $\Delta H$  and  $\Delta G$  were evaluated using the  $\Delta E_{\text{ele-nuc}}$  from the BLYP/6-31G(d,p)//PM3 calculation and the  $\Delta E_{\text{int}}$  and  $\Delta G_{\text{T}}$  from PM3 full geometry optimization (frequency calculation) level. <sup>d</sup> The S and SS labels stand for sandwich and super-sandwich interactions, respectively, as depicted in Figure 3. <sup>e</sup> Perpendicular-like structure as proposed in ref 24.

interaction energy rises to  $3.55 \text{ kcal}\cdot\text{mol}^{-1}$ , as the dimerization is unfavorable compared to the free monomers. This effect is opposite when TT and HT configurations are considered. For TT, the interaction energy is decreased from  $27.6$  (TT) to  $7.79 \text{ kcal}\cdot\text{mol}^{-1}$  (TTSS) and for HT from  $44.8$  (HT) to  $23.5 \text{ kcal}\cdot\text{mol}^{-1}$  (HTSS). These results show that only the species HH and HHS should be stable relative to the free hexahydrated monomers. The formation of the isomer TTSS is thermodynamically favorable ( $\Delta G = -0.21 \text{ kcal}\cdot\text{mol}^{-1}$ ); however it is less stable than the two free monomers by  $7.79 \text{ kcal}\cdot\text{mol}^{-1}$ .

Different from the  $\alpha$ -CD monomer case, there is no experimental enthalpy and entropy data available for comparison. However, the good agreement reported in ref 26 for the  $\alpha$ -CD hydration process adds confidence to the methodology used here, also bearing in mind that we are comparing relative thermodynamic property values and not concerning with absolute Gibbs free energy data. Therefore, the predominant process, among the nine possibilities, can be unambiguously determined on solid basis. Our results show that on a Boltzmann or Gibbs distribution basis only HH dimer type structures would be observed, with the HH mode of interaction, with no water tetramer intercalating two  $\alpha$ -CD monomers, being the most favorable. Recently a very interesting work was published by Miyake et al. concerning the formation process of cyclodextrin necklace, analyzing the hydrogen bonding on a molecular level, using scanning tunneling microscopy.<sup>45</sup> In their work, the molecular necklace consisted of the six glucose units of the  $\alpha$ -CDs threaded on a poly(ethylene glycol) (PEG) chain. They concluded that about 20% of the HT conformation was found to exist, contrary to the HH and TT commonly accepted as the dominant modes of interaction. The results obtained using our model for the hydrated  $\alpha$ -CD dimer may be compared with the results reported in ref 45. It can be seen from Table 2 that, on the basis of the relative Gibbs free energy results, a possible  $\alpha$ -CD multimeric structure somehow similar to the molecular necklace observed in ref 45 would consist basically of the HH and TT type structures. The HT spatial arrangement is unfavorable in relation to the TT structure by ca.  $17 \text{ kcal}\cdot\text{mol}^{-1}$ , with the corresponding values for the HTS/TTS and HTSS/TTSS structures being respectively 7 and  $16 \text{ kcal}\cdot\text{mol}^{-1}$  respectively ( $\Delta G$  values were considered). On the basis of our theoretical results for the  $\alpha$ -CD dimer hydrate, we would not anticipate an experimentally detectable presence of the HT mode of interaction in a  $\alpha$ -CD nanotube-like structure containing water tetramers as spacer group if the HH dimeric structure is considered as basic unit. Furthermore, the point must be raised that the

thermodynamics of formation of larger oligomers might be distinct from the simple dimer association. The PEG chain may also play an important role for the stabilization of the HT structure yielding a relative proportion of 20%, which was detected in the experiment reported in ref 45. A theoretical investigation of the molecular necklace structure addressed in ref 45, using the same approach proposed in this work, would be very interesting to carry out, and an explanation for the presence of the HT structure on a molecular level basis would most probably emerge.

## Conclusion

In this article, nine possible molecular structures for the dimer formed by  $\alpha$ -CD hexahydrate subunits were investigated using a combined DFT/semiempirical level of theory (BLYP/6-31G(d,p)//PM3), which can satisfactorily describe the H-bond interactions that play a major role for the dimer stabilization. The fully optimized equilibrium minimum energy structures (characterized by having real harmonic frequencies) have a water dimer structure situated inside the cavity, very close to the center of mass, and a water tetramer surrounding the two ends. The HH mode of interaction is preferred over the HT and TT ones, having a Gibbs free energy of formation value of  $-27.02 \text{ kcal}\cdot\text{mol}^{-1}$ , considerably larger than the value reported for the  $\alpha$ -CD hexahydrate structure ( $\Delta G = -4.0 \text{ kcal}\cdot\text{mol}^{-1}$ ). However, when water tetramers are trapped between two  $\alpha$ -CD monomers, functioning as an intercalating agent, the HH configuration is destabilized and TT structures stabilized (now denominated HHSS and TTSS), having both negative  $\Delta G$  values, opening the possibility of a double inclusion complexation with guest molecules, perhaps enhancing the encapsulating capacity of the  $\alpha$ -CD. Our results provide a strong motivation for investigating the structure of  $\alpha$ -CD molecular nanotubes, having water tetramers as spacer group, instead of the PEG chain in the formation process of cyclodextrin necklace reported recently. Our group is already engaged in such theoretical investigation.

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