α-, *β*-, and *γ*-Cyclodextrin Dimers. Molecular Modeling Studies by Molecular Mechanics and Molecular Dynamics Simulations

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The α-, *β*-, and *γ*-cyclodextrin (CyD) dimers have been studied by molecular mechanics (MM) and molecular dynamics (MD) calculations, and the relative stability of dimers and the involved molecular interactions have been determined. Three possible orientations were considered for the α-, *β*-, and *γ*-CyD dimers: the head-to-head, the head-to-tail, and the tail-to-tail. In vacuo MM calculations were used to obtain the most stable arrangements, and MD simulations were performed over all energy minima obtained for each dimer. Results from MD always show head-to-head orientation as the most stable as a result of the larger number of intermolecular hydrogen bonds present.

Introduction

Cyclodextrins (CyDs),[1] cyclic oligomers of glucose, and their derivatives have been widely studied[2,3] because of their use as hosts in molecular recognition.[4] Each CyD molecule is composed of several glucose residues linked by α-(1,4) glycosidic bonds.[5,6] Although CyDs with up to 12 glucose residues are known, only the first three homologues (α-, *β*-, and *γ*-CyD with six, seven, and eight glucose residues per macrocycle, respectively) have been studied in this work. Sugars normally adopt a $^4C_1$ chair conformation, and in CyDs they are oriented generating a toroidal/hollow truncated cone structure.[7] Ratios between CyD and substrate are 1:1[8,9] or 2:1[10−12] for most compounds, although some cases of 2:2 stoichiometries have also been detected.[13] The inclusion compounds composition critically depends on the types of CyD and on the physicochemical properties of the involved guest.

Many have studied either isolated CyDs or their 1:1 inclusion complexes by computational techniques.[14] The formation of 2:1 or 2:2 complexes requires the association of two CyD units. The formation of aggregates in aqueous solution of pure CyDs has been experimentally detected,[15] but the driving force for this aggregation has never been systematically studied.[16] This paper shows that the number of hydrogen bonds formed between both CyD units is the driving force responsible for the dimer formation. Three possible orientations between CyD units have been studied by molecular mechanics (MM) and molecular dynamics (MD) calculations: the head-to-head, the head-to-tail, and the tail-to-tail (Figure 1) (hereinafter called HH, HT, and TT, respectively). Results point toward the HH orientation as the most stable for the three native CyDs studied.

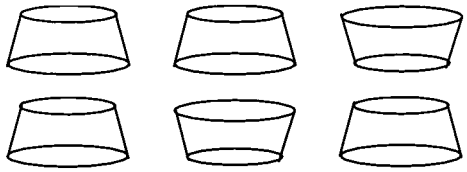

Figure 1. The three orientations studied for α-, *β*-, and *γ*-CyD.

Results and Discussion

The building of the CyD dimers was performed using the available crystallographic data[17−19] of each monomer as the starting conformation. To begin the study, the CyD monomers were arbitrarily located at a distance of 18 Å between the molecular centroids (calculated with respect to all of the glycosidic oxygen atoms). The two CyDs were brought closer by decreasing their separation in 1 Å steps until the distance is 2 Å by using an in-house program.

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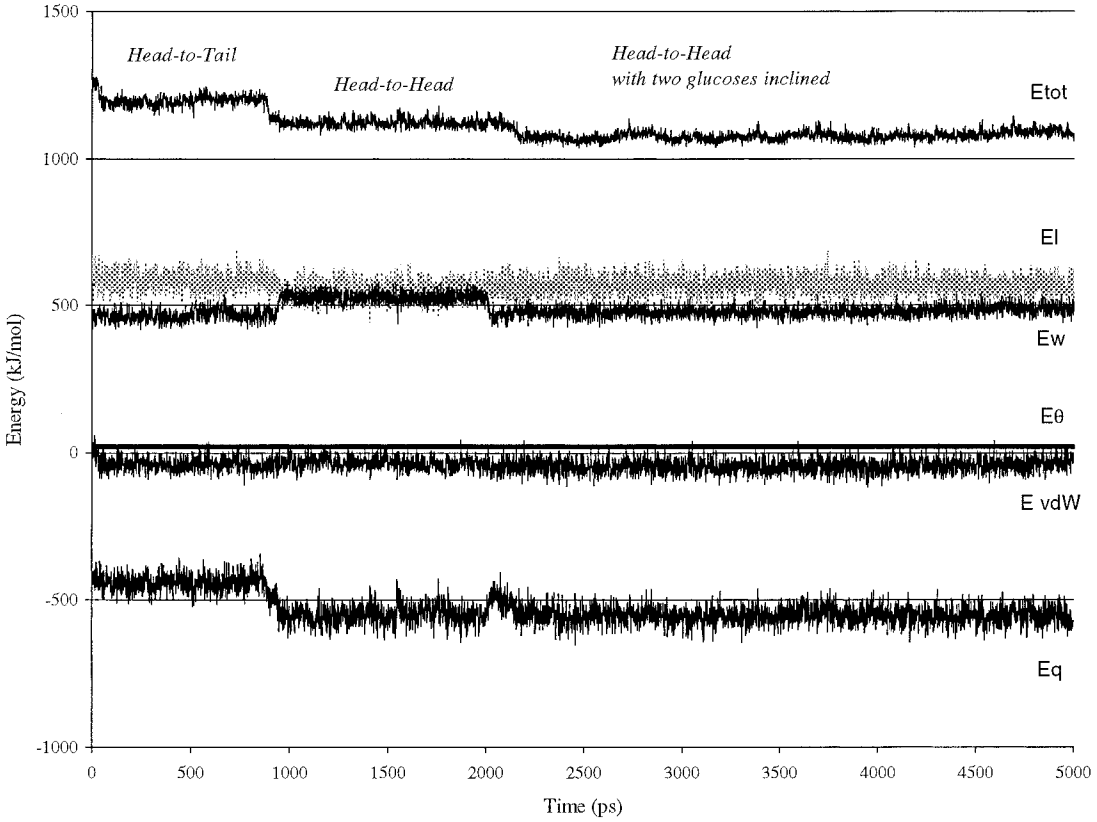

Figure 2. Variation of the energies (stretching, E_l; bending, E_θ; torsion, E_ω; van der Waals, E_{vdw}; electrostatic, E_q; and total, E_{tot}) obtained in the MD simulation for the α-CyD starting at tail-to-tail orientation (see text).

After each approach of 1 Å, the conformation of the dimer was minimized using the original MM3(92)[20] force field.[21] Three glycosidic O atoms of one of the CyDs were fixed in the *x*, *y*, and *z* axes to prevent the movement of one unit, while only one glycosidic O atom was fixed in *x*, *y*, and *z* on the other CyD to maintain the distance between the two CyDs units. On the other hand, one of the CyDs was rotated 36 times using a step of 10° to cover all possible relative orientations between both monomers in each of the nine dimers (three orientations for the three CyDs).

The analysis of the potential energy surfaces corresponding to this closing-up and rotation of the CyD dimers shows several energy minima at different combinations of rotation angles and distances. MM3 calculations indicate that formation of the HH orientation is the most energetically favored for α- and β-CyD, while for the γ-CyD it is the TT orientation. The energy of binding has been considered as the difference between the most stable minimum and the energy for the monomers separated by 18 Å. Values (−130.6, −208.5, and −171.6 kJ/mol for α-, β-, and γ-CyD, respectively) are essentially due to both van der Waals and dipole−dipole energy terms. Interestingly, MM calculations indicate that the energy coming from dimerization of β-CyD will be larger than that for α- and γ-CyD at any orientation, in agreement with available experimental results that suggest a preferred molecular aggregation for β-CyD as compared with α- and γ-CyD.[15]

Molecular dynamics (MD) simulation runs were performed over each of the energy minima obtained by the preceding strategy. AMBER* force field[22,23] as included in the Macromodel V.5 package[24] was used for the MD simulations. Cutoff radii for van der Waals and Coulombic electrostatic interactions were 8 and 20 Å, respectively. All C−H and O−H bond lengths were held fixed using the SHAKE[25] algorithm. All MD runs were started with an initial temperature of 5 K, thus initializing the atomic velocities that optimized the coordinates of the system for the simulation start. Four consecutive molecular dynamics steps were executed in all cases. Dimers were warmed from 50 to 150 K during 10 ps. The simulation was run over a period of 10 ps and then equilibrated for 100 ps. During the production simulations of 5000 ps length, structures were saved to disk every 1 ps resulting in 5000 saved structures from each trajectory. The MD simulation had a time step of 0.5 fs during the heating step and 1 fs during the equilibration and production at 298 K. Translational and rotational momentum were removed every 0.1 ps.

Long molecular dynamics runs have been performed (5000 ps) for all three CyDs and orientations, and no significant differences were obtained between each other. As an example, Figure 2 depicts the energy variation experienced by one of the α-CyD energy minima (initial

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Table 1. Summary of Data Obtained for the α-, *β*-, and *γ*-CyD Dimers

	tail-to-tail	head-to-tail	head-to-head
α-CyD		with 2 glucoses inclined:	with 2 glucoses inclined:
MD total energy (kJ/mol)	1215	1124	1070
distance (Å)	9.2	6.6	5.8
ave no. of intermolecular H bonds	1.76 ± 1.14	4.24 ± 1.31	8.14 ± 1.82
mean values of the energy minima[a] (kJ/mol)	388.5	401.4	355.3
β-CyD			
MD total energy (kJ/mol)	1340	1330	1250
distance (Å)	6.9	6.9	6.9
ave no. of intermolecular H bonds	1.84 ± 1.35	3.39 ± 1.74	9.38±1.92
mean values of the energy minima[a] (kJ/mol)	440/2	432.1	330.7
γ-CyD			with 4 glucoses inclined:
MD total energy (kJ/mol)	1560	1515	1475
distance (Å)	8	7.1	6.4
ave no. of intermolecular H bonds	1.46 ± 1.07	4.12 ± 1.68	7.89 ± 1.98
mean values of the energy minima[a] (kJ/mol)	450.3	543.4	516.6

[a] Obtained by MM using the Boltzmann distribution at 298 K over all obtained minima.

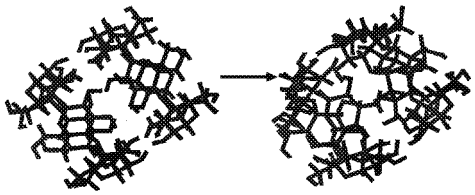

Figure 3. Structure for the α-CyD after 1000 and 4000 ps of the MD production simulation.

orientation was TT having a distance of 8 Å between the two CyDs and a rotation angle of 0°) during the MD simulation. The two CyD units moved during the warming up steps of the run because they already get a perpendicular orientation at the beginning of the production simulation (see Supporting Information for the snapshots of the structures). About 20 ps later in the trajectory, the energy decreases and starts to stabilize: the dimer takes a HT orientation. When the simulation arrives close to 900 ps, the energy decreases again, and the system can be considered as in equilibrium for 2250 ps. During this period, the two CyDs adopt an HH orientation (Figure 3). At this point, the energy decreases once more. This stabilization is due to the movement of two, three, or four glucoses for the α-, *β*-, and *γ*-CyDs, respectively; this can be confirmed from the observation of the energy analysis in Figure 2. Only the electrostatic energy (E_q) and torsion energy (E_ω) fluctuate like the potential energy (E_p). Thus, hydrogen bonds between CyDs are likely to be present and are possibly responsible for the final orientation of the two CyD units during the MD. The analysis of the MD sampling shows the presence of stabilizing [O−H····O] interactions between alcohol groups located at proper distances ≤ 2 Å (see Figure 4). It is worth noting here that the van der Waals energy (E_{vdw}) does not significantly change during the whole simulation, in clear contradiction with what was observed by the MM3 calculations. This difference is due to the electrostatic approach used in these force fields. The MM3 model was developed on the basis of the point dipole approach for estimating the intramolecular electrostatic interactions. This model has not been rigorously established as a general model for modeling intermolecular interactions. In contrast, AMBER model is based on atomic centered charges that fit the ab initio computed molecular electrostatic potential for estimating the intermolecular electrostatic interactions.

Plotting the distance between both CyD centroids versus the simulation time can monitor the movement of the two CyDs. Clearly, they tend to approach each other as the result of the formation of several intermolecular hydrogen bonds.

MD simulations performed over any of the considered orientations for the *β*- and *γ*-CyDs present similar trends for the potential energy (E_p) as the one shown in Figure 2. Interestingly, a larger distortion of the *γ*-CyD dimers (see Supporting Information for Cartesian coordinates and snapshots of the structures) is observed because of the larger flexibility of this CyD when compared with smaller CyDs. Moreover, in its HH orientation at least two glucose units are always turned over for each *γ*-CyD, thus favoring a closer contact between the CyD fragments, and enhance the van der Waals' stabilization. This fact is also found in *ϵ*-, and *ι*-CyD (formed by 10 and 14 glucose units, respectively). Their shape (bowl) is due to two diametrically opposed glucoses in a trans orientation, with respect to the rest of glucoses, disrupting the intramolecular hydrogen bonds.[26]

Results of all MM and MD simulations are summarized in Table 1. The starting point for the MD simulations has been shown to be not crucial because identical final energy and structure were obtained for each orientation (HH, HT, and TT) independently of the starting rotation angle. Figure 5 graphically depicts a summary of all results obtained within this work. When the MD simulation starts at a TT orientation (in any of the CyD dimers), very often the orientation changes to the HT, and then sometimes the dimer changes to the HH orientation. Interestingly, reverse processes (HH → HT or HT → TT) have never been observed during our simulation times.

MD simulations suggest that α-CyD slightly prefers the HH orientation over the HT (by 52 kJ/mol), with HH having double the number of intermolecular hydrogen bonds as HT (see Table 1). Its TT orientation is the least stable (91 kJ/mol over the HT) and forms the smaller number of intermolecular hydrogen bonds (about only one). *β*-CyD presents the HH orientation as the most stable (80 kJ/mol below HT and 90 kJ/mol below TT), and their number of intermolecular hydrogen bonds (about nine) is the largest among all the computed dimers. *γ*-CyD also presents the HH dimer as the most stable (40 kJ/mol below HT and 85 kJ/mol below TT), forming about eight intermolecular hydrogen bonds.

The binding energy has been estimated from the

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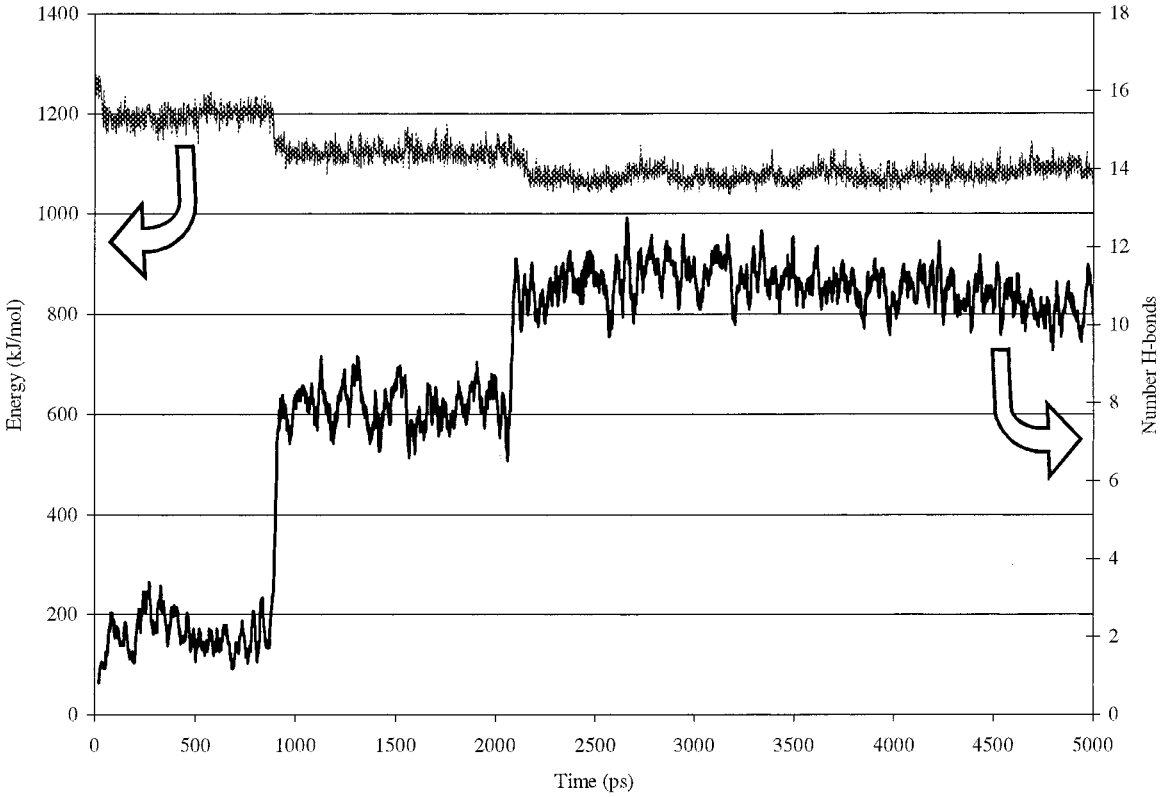

Figure 4. Variation of the total energy (kJ/mol) and of the number of intermolecular hydrogen bonds during the MD simulation for the α-CyD starting at tail-to-tail orientation, as an example.

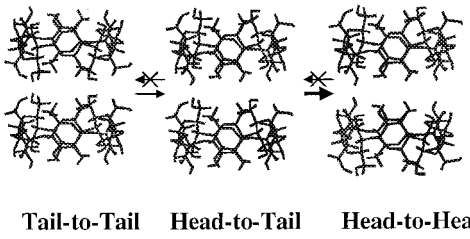

Figure 5. Schematic summary of the evolution of the orientation for the CyD dimers (represented by α-CyD as an example). Arrow thickness indicates the probability of the process. Crossed arrows indicate that the process has never been observed during our MD simulations.

difference between the MD total energy of two isolated CyD units and that for the dimer in its most stable orientation (HH). α- and *β*-CyD present a binding energy of about −217.7 kJ/mol (−210 and −225 kJ/mol, respectively), while *γ*-CyD has a smaller value (−196.7 kJ/mol), in agreement with those obtained from MM calculations.

Our calculations have been carried out in the absence of solvent. CyD dimers will definitely interact with solvent molecules (usually water). Two isolated monomers would very probably present larger solvation ΔH than one dimer because there are almost double number of hydrophilic interactions. Moreover, the ΔS for the solvation should also favor the monomers. The question is thus if these solvent−solute interactions will compensate the computed stabilization of about 126−209 kJ/mol for the dimerization.

Conclusions

The three more common CyDs dimerize (in vacuo) in the HH orientation due to the number of intermolecular hydrogen bonds formed (1−2 for the TT, 3−4 for the HT, and 8−9 for the HH) as obtained by our MD simulations. The dimerization binding energy is computed to be around 126−209 kJ/mol, depending on the CyD and orientation. The structure of *β*-CyD does not change much on dimerization. Interestingly, *γ*-CyD dimers contain two diametrically opposed glucose units not aligned with the rest of the glucose units, in agreement with the experimental results found for *ϵ*- and *ι*-CyD. This finding suggests that this phenomenon is general among CyD systems.

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Supporting Information Available: Snapshots and Cartesian coordinates (corresponding to the structure at 4000 ps) for the *γ*-CyD dimer MD simulation starting in the TT orientation. This material is available free of charge via the Internet at http://pubs.acs.org.

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