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Capacity of small molecules to form β-cyclodextrin inclusion complexes

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Capacity of small molecules to form β-cyclodextrin inclusion complexes

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The mobility of atoms and cyclic or spherical guest molecules inside and around β-cyclodextrin (β-CD) is analysed, along with the influence of temperature on inclusion complex formation, by means of a molecular dynamics simulation at constant temperature. The intermolecular energy is modelled by a Lennard-Jones potential and a continuum description of the cavity walls. The potential energy parameter σ principally determines the mobility of the guest inside the cavity in the CD, the preferred position and the probability of forming an inclusion complex, while the parameter ε is responsible for the guest staying inside or exiting from the cavity after the inclusion time. The probability of entering increases with the temperature of the process.

Keywords: inclusion complex; potential energy surfaces; computer simulation; molecular mechanics; molecular dynamics

1. Introduction

In the previous work we proposed an analytical model for the interaction energy between α-, β- and γ-cyclodextrin (γ-CD) with guest molecules of different structures and sizes (*1*). The intermolecular energy was then modelled by a Lennard-Jones potential, which represents the attractive and repulsive interactions between all atoms and molecules in the system, and a continuum description of the cavity walls (*2*, *3*). The difference in the molecular size was represented in that study by the potential energy parameter σ, but without including any parameter related to the structure of the guest molecules. This simple model is able to reproduce several quantitative and qualitative features of the interaction energy between CD and atoms, and cyclic or spherical guest molecules. The adsorption energy obtained from this model is only valid when the guest's centre of mass is located along the cavity axis, because for points away from it there is no analytical solution for the energy. Therefore, this analytical model is inadequate to analyse the mobility of these types of molecules around β-CD and even inside the cavity, because the guest does not always move along the axis.

Our aim in the present study is therefore firstly to calculate the interaction energy between the β-CD and the guest molecule inside and outside the cavity, not only along the axis, using a simple pairwise-additive Lennard-Jones potential and a continuum description of the cavity walls. The Lennard-Jones potential represents the attractive and repulsive interactions which act between all atoms and molecules, even totally neutral ones, in contrast to the other types of forces that may or may not be present depending on the properties of the molecules, such as electrostatic charges, dipoles or hydrogen bonds. Since continuity is assumed for the guest and the cavity, the interaction energy presented in this work is not capable of reproducing the hydrogen bonds formed by the guest molecule with CD. However, the van der Waals term is the main contribution to the total energy, particularly inside the cavity and so directly determines the configuration of the inclusion complex. To take into account the effects of the solvent, other interaction energies must be applied.

We also examine the influence of temperature on inclusion complex formation by means of molecular dynamics (MD), since this simulation method is based on the resolution of classical equations of motion to determine the trajectories of the particles depending on the initial conditions (*4–6*). By treating the results generated in this process with the statistical methods, one can obtain a more detailed information about the potential parameters related to the size and composition of the guest molecule that influence the formation of inclusion complexes with β-CD. In Section 2, we present the theoretical methods and in Section 3, their main results.

2. The model

2.1 *Expression of the interaction potential*

The intermolecular energy is modelled by a Lennard-Jones potential, which represents the attractive and repulsive interactions between all atoms and molecules in the system, even totally neutral ones. The essential effects of the confinement should be preserved if we make the assumption of a continuum description of the cavity walls (*1–3*), therefore the interaction energy W can be calculated

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as

$$W(\vec{r}_{\mathrm{mol}}) = \rho_{\mathrm{CD}} \int_S V(\vec{r}_{\mathrm{mol}}, \vec{r})\, \mathrm{d}\vec{r}, \qquad (1)$$

where the guest molecule–CD interaction is represented by an average over the uniformly distributed atoms in the CD. ρ_{CD} is the superficial density of atoms in the CD cavity, $\vec{r}_{\mathrm{mol}}$ is the position of the centre of mass for the guest molecule and $\mathrm{d}\vec{r}$ is the differential element of the surface (on the cavity) located at $\vec{r}$. The CD is considered as a truncated cone, h being the axial length ($h \approx 7$ Å), b the radius of the larger base of the cone ($b \approx 5$ Å for β-CD) and a the radius of the smaller top ($a \approx 4$ Å for β-CD) (*7*). Here, the *Z*-axis is collinear with the cone axis (thus the *XY* plane is parallel to the cone base), and the origin of the coordinates lies at the centre of the cavity. When we consider the interaction energy W by the integration in Equation (1), we are substituting the discrete atoms of the CD by a uniform distribution of mass on the cavity surface. Therefore, we can also replace the potential parameters for the different atoms belonging to the molecule $(\sigma_i, \varepsilon_i)$ and β-CD $(\sigma_j, \varepsilon_j)$ by some representative values for the composition of both systems. In order to bring out more clearly the dependence of W on the composition of the guest molecule, we do not consider the values of these parameters for β-CD and the guest separately, but represent the Lennard-Jones parameters for the interaction between the atoms of the CD and the molecule by σ and ε. As we are dealing with a conical continuum geometry, for every plane $Z =$ constant, the potential energy is the same for points (x_0, y_0) located at the same distance d from the cavity axis $(x_0^2 + y_0^2 = d^2)$, for this reason we characterise the guest's centre-of-mass position by the distance d from the cavity axis and the Z coordinate.

The potential energy is determined by Equation (1) for different positions of the guest's centre of mass $\vec{r}_{\mathrm{mol}}$, inside and outside the CD. In each plane $Z =$ constant, about 500 points are explored and the range of variation along the *Z*-axis is about 10 Å. The results obtained are represented by the potential energy surfaces, penetration potentials and the inclusion complex configuration, as in the previous works (*1–3*). The curve joining the minimum potential energy for every plane $Z =$ constant defines the penetration potential, which describes the variation in interaction energy when its path through the cavity is non-axial. The position of the guest molecule for which we obtain the absolute minimum potential energy gives the geometry of the inclusion complex.

The potential energy surfaces are represented by partitioning the variation range of the *Z*-axis in the β-CD cavity into four parts, depending on the position of the guest molecule's centre of mass near the top of the cone (region I), near the centre of the cavity (regions II and III) and near the cone base (region IV). The length of each domain is about 2 Å and the potential surface for each region is determined as the minimum energy for every point on the plane in the corresponding interval of *Z*.

2.2 Simulation method

MD is based on the resolution of classical equations of motion to determine the trajectories of the particles, depending on the initial conditions. The initial conditions of the guest molecule are in this case determined by the centre-of-mass position and velocity. The magnitude of the initial velocity depends on the temperature of the process, but its direction in each trajectory and the initial centre-of-mass position are determined randomly. The simulation time for each trajectory is 1 ns with a step of 1 fs and the configuration and energies (kinetic and potential) were written every 100 steps. We use an in-house program written in Fortran and the equations of motion to perform constant temperature MD are integrated numerically using a variant of the leap-frog scheme (proposed by Brown and Clarke) (*8*), constraining the rotational and translational kinetic energies separately (*9*).

To determine the preferential binding site of the guest molecule, the number densities of presence in a volume element are calculated. We define a grid in which the distance between two consecutive points is 0.5 Å and the number of guest positions in each volume element is the resulting number density for each trajectory and for the guest (*10–12*). The position probability density is calculated by dividing the number density in a volume element by the total number of centre-of-mass positions of the guest.

We calculate different trajectories with the initial configurations of the guest on the exterior of the β-CD: near the primary (narrow end) and secondary rims (wide end) of the CD, and outside the cavity walls. However, the molecule can enter the cavity and then form an inclusion complex only for certain initial positions of its centre of mass, and these positions are always near the rims of the CD and never outside the cavity walls. To calculate the probability of forming an inclusion complex P_{inc}, we determine the external configurations on the grid from which the molecule can enter the cavity. The rate of these positions with respect to the total number of points on the grid is the corresponding probability.

The simulation is carried out for molecules with different sizes and compositions, and at different temperatures.

3. Results and discussion

3.1 Interaction energy

The interaction energy, *W*, depends on the size and composition of the guest molecule through the potential parameters (σ, ε) and the position of its centre of mass $\vec{r}_{\mathrm{mol}}$.

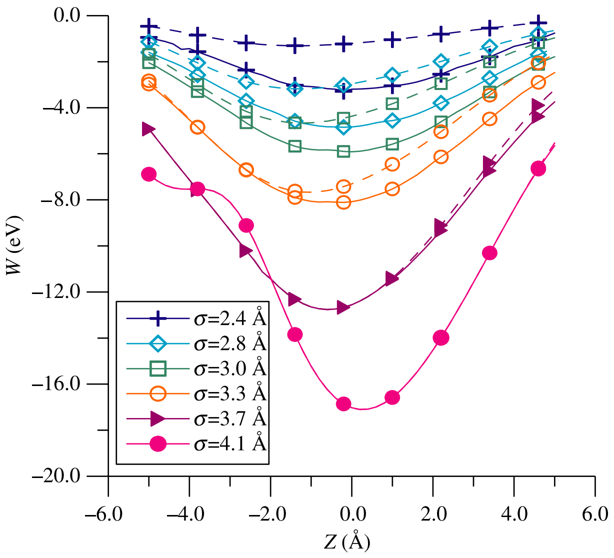

Figure 1. The penetration potential (solid curves) and the interaction energy along the cavity axis (dashed curves) for the guest molecules with different σ and $\varepsilon = 0.006$ eV.

In order to perform a comparative study, we consider different values for the parameter σ to represent the interaction between the β-CD and the guest, because ε only acts as a scaling factor on the potential energy W.

Figure 1 exhibits the penetration potential (solid curves) for the guest molecules of different sizes and compositions. It clearly resembles a well potential, deepening as the atomic or molecular size of the guest increases, and with small differences in the Z coordinate (near the cavity centre) of the minimum values W_{min}. This behaviour is similar to the well potential for the interaction between a guest molecule and the CD, obtained by the sum of pairwise-additive potentials (as in molecular mechanics calculations) (*13*), and it means that the guest molecule positions inside the cavity are more stable than outside the β-CD. Figure 1 also exhibits the interaction energy along the cavity axis (dashed curves). The two curves are seen to agree for molecules with $\sigma = 4.1$ Å, as the size of the guest decreases there are some small differences in the energy values near the larger base of the β-CD, and for small guest molecules the penetration potential is very different from the energy on the axis because in this case the most stable molecular positions are located near the cavity walls. There are also greater differences in the values of W on the potential surface as the guest increases.

The centre-of-mass position at the minimum energy W_{min} is determined by $\left(d_{\mathrm{min}}, z_{\mathrm{min}}\right)$ (Table 1), and it can be seen that the distance between this position and the cavity axis d_{min} depends on the parameter σ by $D_{\mathrm{min}} = 1.12\sigma$, $D_{\mathrm{min}} = u(z_{\mathrm{min}}) - d_{\mathrm{min}}$ being the distance between the cavity walls and the molecule in the more stable configuration and $u(z_{\mathrm{min}})$ being the cone radius at the z_{min} coordinate, as occurs in the continuum model for the interaction between a linear molecule and the β-CD (*2*, *3*). Therefore, the part played by the potential parameters in the interaction energy W is similar to that in the Lennard-Jones potential between a pair of atoms: ε governs the strength of the interaction and σ is related to the position of the minimum energy ($r_{\mathrm{min}} = 1.12\sigma$) (*14*). The σ parameters selected in this work are of the same order of magnitude as pairs of atoms like C–C, C–O, O–O, etc. and the minimum interaction energy between them at the equilibrium position is $-\varepsilon$ (about -0.008 eV for such pairs) (*14*). If we consider this ε value for the interaction between the cyclic or spherical molecules and the cavity, the minimum energy W_{min} ranges from -4.3 eV for $\sigma = 2.4$ Å to -22.8 eV for $\sigma = 4.1$ Å, therefore the confinement in β-CD involves a more intense interaction, greater even than for linear molecules (*2*, *3*). For instance, if we apply the present model to cyclopentadiene, taking into account the results obtained by a force field method (*13*), it can be represented by the parameters $\sigma = 3.5$ Å and $\varepsilon = 0.0004$ eV, ε being five times less than for linear molecules such as acrylonitrile or methyl vinyl ketone. In Table 1, some samples of the atoms and molecules are included along with some parameters that simulate the interaction between β-CD and these guest molecules (*13*, *15*, *16*). However, the interaction energies presented in this table are obtained with $\varepsilon = 0.006$ eV, since ε only acts as a scaling factor on the potential energy W, these binding energies are about 10 times bigger than the values corresponding to real cyclic or spherical molecules.

Table 1. The minimum energy W_{min}, the centre-of-mass position in the minimum energy $\left(d_{\mathrm{min}}, z_{\mathrm{min}}\right)$ and the cone radius at the z_{min} coordinate for the guest molecules with different σ and $\varepsilon = 0.006$ eV.

Atoms and molecules	σ (Å)	W_{min} (eV)	d_{min} (Å)	z_{min} (Å)	$u(z_{\mathrm{min}})$ (Å)
Xe	2.4	−3.20	2.01	−0.2	4.48
Acrylonitrile, cyclopropane	2.8	−4.85	1.50	−0.2	4.48
	3.0	−5.95	1.23	−0.4	4.46
Cyclopentadiene, benzene, aromatic rings	3.3	−8.20	0.82	−0.2	4.48
	3.7	−12.76	0.00	−0.6	4.43
α-Pinene, limonene	4.1	−17.10	0.00	0.2	4.54

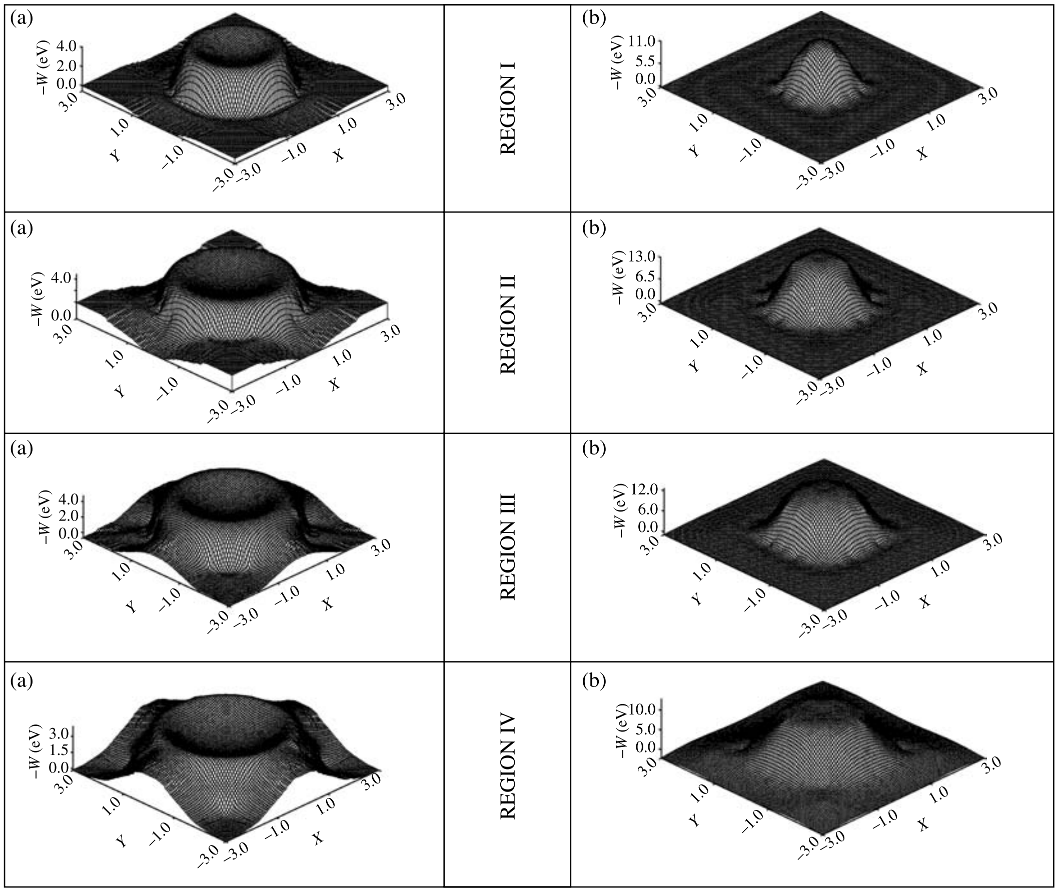

Figure 2. The potential energy surfaces for atoms, cyclic or spherical molecules with different σ and $\varepsilon = 0.006\,\text{eV}$: (a) $\sigma = 2.8\,\text{Å}$, (b) $\sigma = 3.7\,\text{Å}$.

Figure 2 shows the potential energy surfaces for atoms, cyclic or spherical molecules with $\sigma = 2.8\,\text{Å}$, $\varepsilon = 0.006\,\text{eV}$ (Figure 2(a)) and for $\sigma = 3.7\,\text{Å}$, $\varepsilon = 0.006\,\text{eV}$ (Figure 2(b)). They are similar in the size of the regions where the energy is attractive, this feature being a consequence of the cavity geometry. The main differences in the potential energy surfaces are related to the magnitude of the energy, which is largely dependent on the molecular composition rather than its geometry, as occurs in the continuum model for the interaction between a linear molecule and the β-CD.

Comparing the intermolecular potential presented in this study with the results obtained by the all-atoms model, the main discrepancies derive from the position of the guest's centre of mass in the configuration of the inclusion complex, because this continuum model is only able to reproduce the position in the plane $Z = \text{constant}$ by the distance from the cavity axis instead of the (X, Y) coordinates.

3.2 Molecular dynamics

The evolution of the guest molecule in each trajectory and the resultant average energy are different because the initial conditions determine the integration of the equations of motion. The initial velocity does not influence the number densities and the mean energy of the process, but the starting centre-of-mass position determines the behaviour of the guest in each process and decisively affects the probability of forming an inclusion complex. When the guest's initial position is located outside the cavity walls, the molecule always stays on the outside of the β-CD where it does not reach a stable configuration, moving around the cavity continually or even tending to move away. During the trajectories whose starting molecular configuration is near the rims of the β-CD, the guest tends to enter the cavity, remain inside forming an inclusion complex or exit from it after a period, depending on the potential parameters. However, inside the cavity the molecule does not reach a stable configuration because it is fluctuating around the most probable position $\vec{r}_\text{p}$ with an amplitude that also depends on parameters (σ, ε). This effect can be appreciated in Figure 3, which shows the position probability for molecules with different σ and the same ε, and includes a schematic representation of the projections of the cavity in the plane. The range

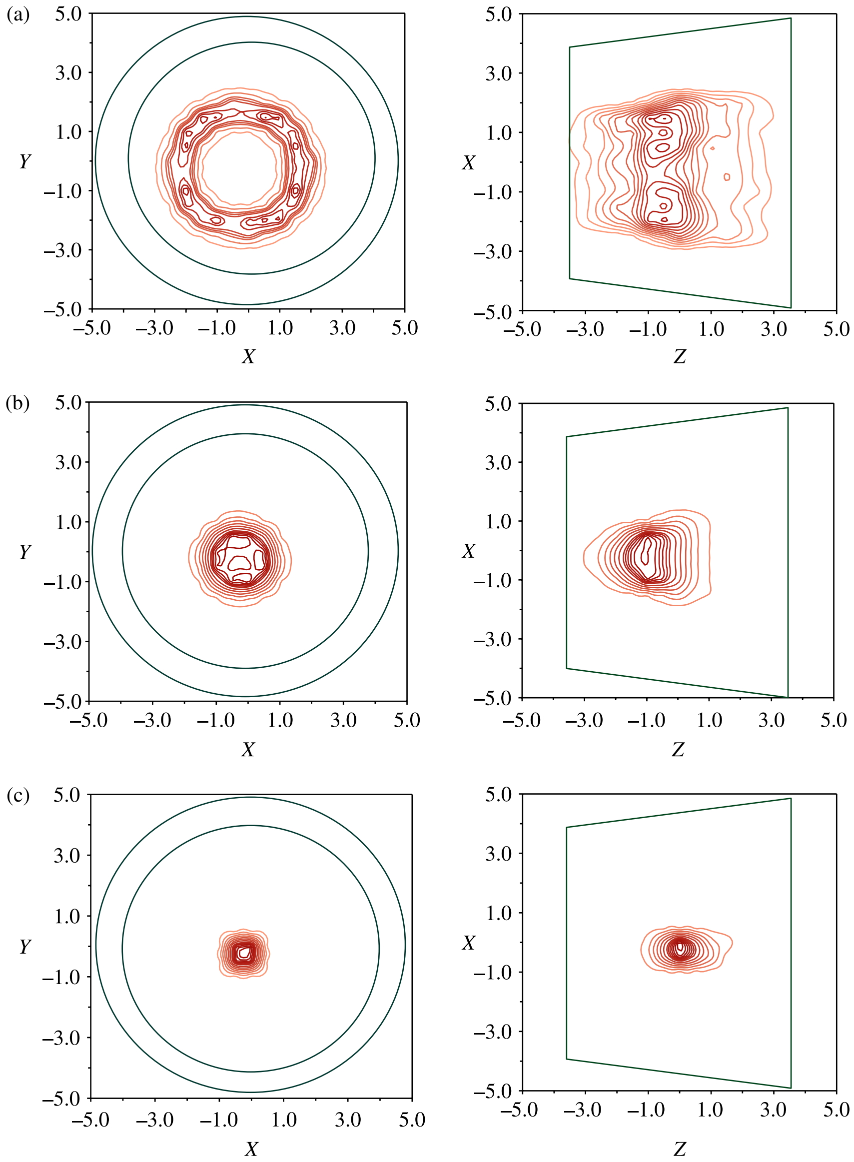

Figure 3. Projections on the *XY* and *XZ* plane of the probability density of presence for guest molecules with different σ and $\varepsilon = 0.006$ eV at temperature $T = 293$ K: (a) $\sigma = 2.4$ Å, (b) $\sigma = 3.3$ Å, (c) $\sigma = 4.1$ Å. They include a schematic representation of the projection of the cavity in the plane.

Table 2. The maximum probability $P_{\max}$, the most probable configuration of the guest $\vec{r}_p = (d_p, z_p)$, the mean energy W_{mean} and the probability of forming the inclusion complex P_{inc} for the simulation of molecules with $\varepsilon = 0.006$ eV at a temperature $T = 293$ K.

σ (Å)	d_p (Å)	z_p (Å)	$P_{\max}$ (%)	W_{mean} (eV)	P_{inc} (%)
2.4	1.80	− 0.5	2.7	− 2.28	4.1
2.8	1.80	− 0.5	9.1	− 3.62	9.6
3.0	1.00	− 0.5	25.1	− 4.23	12.1
3.3	0.71	− 0.5	42.1	− 6.23	23.8
3.7	0.50	− 0.5	68.7	− 9.89	32.6
4.1	0.00	0.00	81.0	− 13.20	65.5

of oscillations inside the β-CD increases as the molecular size decreases, which means greater delocalisation for the guest and thus smaller values for the position probability. The maximum probability $P_{\max}$ and the corresponding position of the guest $\vec{r}_p = (d_p, z_p)$ are presented in Table 2. It can be seen that the most probable configuration ranges from near the cavity walls to the centre of the β-CD as the molecular size increases: so taking into account the method used to calculate the position probability density, we conclude that it corresponds to the minimum energy configuration of the complex in this type of molecule. The mean energy for the simulation W_{mean} of different molecules is

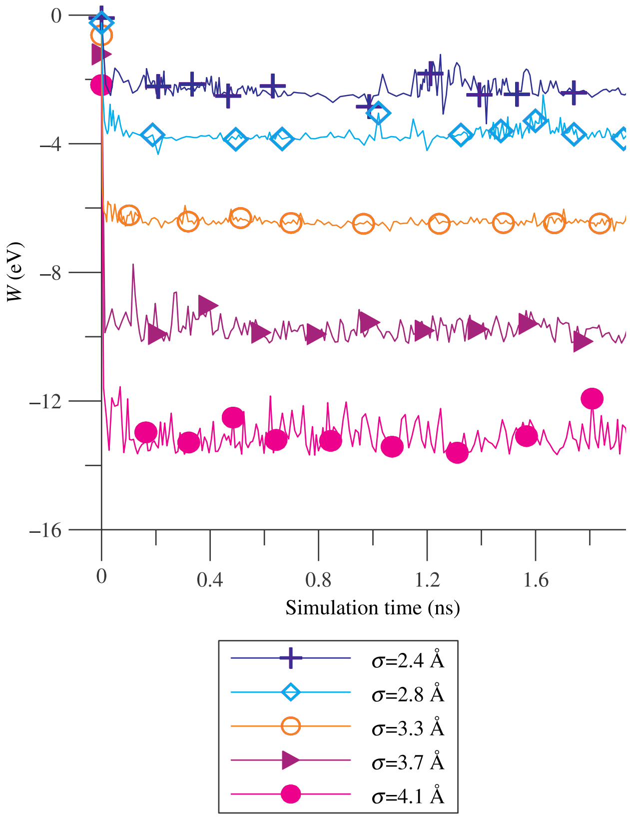

Figure 4. The potential energy during a trajectory for the guest molecules with different σ and $\varepsilon = 0.006\,\mathrm{eV}$.

also presented in Table 2. W_{mean} is greater than W_{min} because the energy of every position with a probability different from zero contributes to the average energy, for bigger molecules there are greater energy differences inside the β-CD and so greater differences from W_{min} (Figure 4). In order to analyse the dependence of the results on the length of the simulation, Figure 4 shows the variations of the potential energy during a trajectory for different guest molecules. There are no great differences between the mean values for 1 and 2 ns (about 4 parts in 1000), however the computer time needed for carrying out the simulation is considerably shorter. If we compare the position probability density for these simulation times, we conclude that the most probable positions are the same and the distribution is similar for each case. But for 2 ns we obtain greater values for the position probability, implying therefore more stabilisation of the system and similar results to 1 ns. We can conclude that a simulation time of 1 ns is adequate for this system.

For molecules with $\sigma \geq 3.0\,\text{Å}$, the parameter ε only acts as a scaling factor in W_{mean} and does not influence the position probability density. For molecules with $\sigma < 3.0\,\text{Å}$, ε affects the amplitude of oscillations around the most probable position: a greater value of the parameter implies smaller fluctuations (Figure 5). The meaning of ε as the strength of the interaction is also reflected in the dynamic behaviour of the system, because while the guest with $\sigma = 2.8\,\text{Å}$ and $\varepsilon = 0.006\,\mathrm{eV}$ remains inside the cavity for the whole simulation time, for $\varepsilon = 0.003\,\mathrm{eV}$ the molecule only spends a period (inclusion time t) inside, after which it exits from the CD and moves away. This t depends on the initial conditions and decreases as temperature increases (the mean inclusion time is 394 ps at 293 K, 381 ps at 323 K and 356 ps at 363 K).

The probability of forming an inclusion complex P_{inc} is presented in Table 2. The differences in P_{inc} are mainly due to the distance from the rims of the β-CD at which each molecule must be located initially to enter the cavity, although in some cases the guest exits from the host after the inclusion time. This distance is usually further from the wide end of the β-CD, and ranges from 3 Å for $\sigma = 2.4\,\text{Å}$ to 6 Å for $\sigma = 4.1\,\text{Å}$. Therefore, considering the same grid around the cavity in all cases, we can conclude that larger molecules have greater probabilities of forming inclusion complexes. P_{inc} is independent of the parameter ε but the temperature T of the process influences P_{inc} decisively, because the magnitude of the initial velocities depends on T and determines the maximum distance from the rims needed by the molecule to enter the cavity. These values for $T = 323\,\mathrm{K}$ are approximately double those for $T = 293\,\mathrm{K}$, this means that P_{inc} increases as T does, although the ratio between the probabilities of different-sized molecules remains similar.

The suitability of the model presented in this work can be confirmed by comparing the results with those of Refs (*10*, *11*), where Lipkowitz et al. studied where and how different analytes bind to the permethylated β-CD in gas chromatography using different computational methods (standard MD and Monte Carlo simulations). The structure of some considered selectands is essentially cyclic and in the case of pinene, the intermolecular forces responsible for holding the host–guest complex are exclusively the van der Waals forces (*17*). They conclude that the preferred binding site for the small analytes is the interior of the macrocycle with rapid shuttling between the primary and secondary rims of the host cavity, in accordance with the results obtained by the model presented in this study.

4. Conclusions

We have studied the mobility of atoms, cyclic or spherical guest molecules inside and around β-CD by the MD simulation at constant temperature. The intermolecular energy is modelled by a Lennard-Jones potential and a continuum description of the cavity walls. It is found that the variation of the potential energy along the Z coordinate (parallel to the cavity

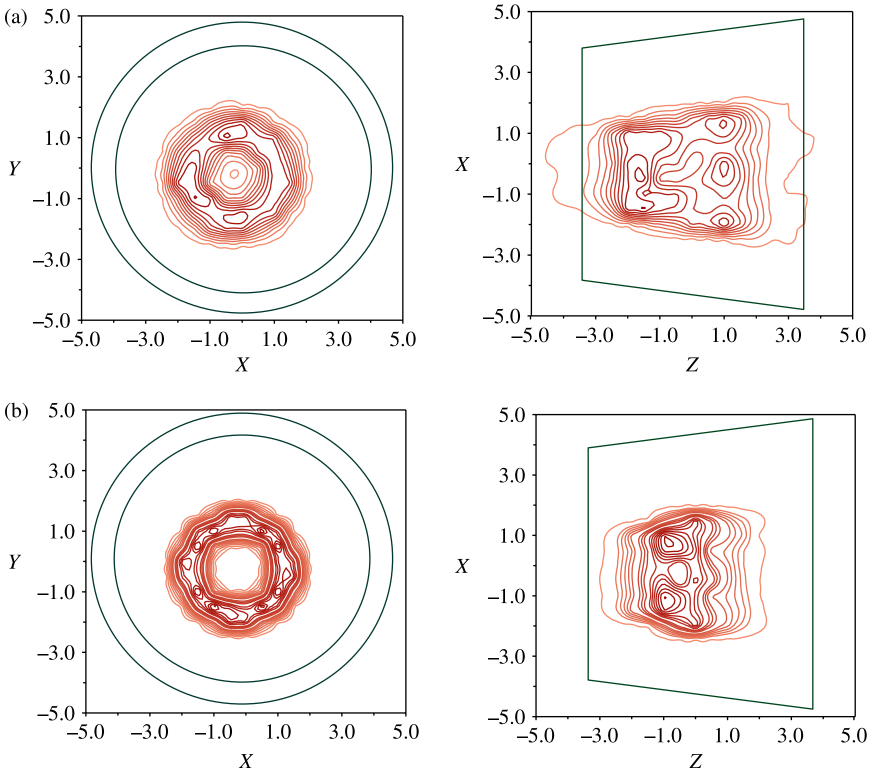

Figure 5. Projections on the *XY* and *XZ* plane of the probability density of presence for guest molecules with different ε and $\sigma = 2.8$ Å at temperature $T = 293$ K: (a) $\varepsilon = 0.003$ eV, (b) $\varepsilon = 0.006$ eV. They include a schematic representation of the projection of the cavity in the plane.

axis) resembles a well potential where the minimum energy is lower as the atomic size of the molecule increases. The distance between the cavity walls and the guest molecule in the absolute minimum energy configuration is approximately 1.12σ and ε governs the strength of the interaction.

In the dynamical study of the system we can conclude that the molecule can enter the cavity and then form an inclusion complex only for certain initial positions of its centre of mass, and these positions are always near the rims of the CD and never outside the cavity walls. The probability of forming an inclusion complex increases with the size of the guest molecule and the temperature of the process. The most probable configuration of the complex formed with cyclic or spherical molecules corresponds to that of the minimum energy. The temperature of the simulation affects the inclusion time spent by the guest inside the cavity, when its interaction with β-CD is represented by parameters $\sigma < 3.0$ Å and $\varepsilon \leq 0.003$ eV.

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