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CAPACITY OF SMALL MOLECULES TO FORM β -CYCLODEXTRIN INCLUSION COMPLEXES

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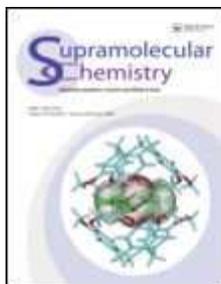
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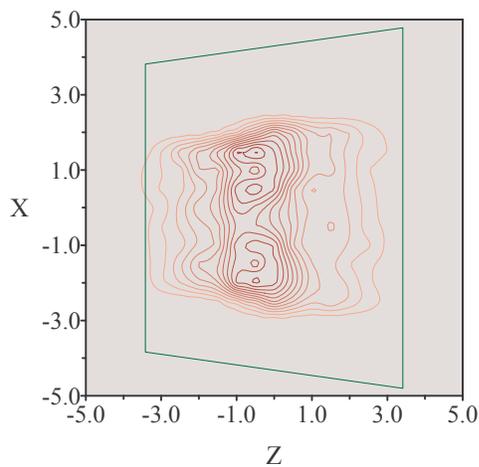
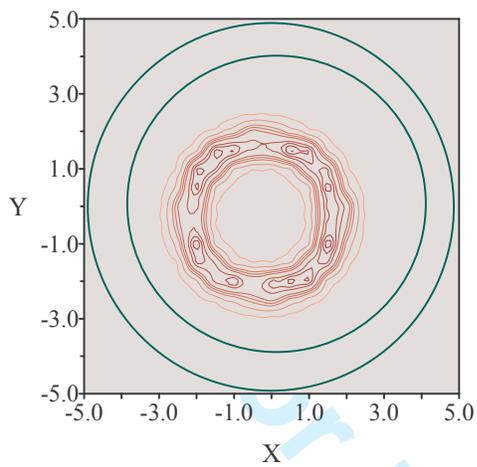
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**CAPACITY OF SMALL MOLECULES TO FORM β -
CYCLODEXTRIN INCLUSION COMPLEXES**

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13 **CAPACITY OF SMALL MOLECULES TO FORM**
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15 **β -CYCLODEXTRIN INCLUSION COMPLEXES**
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Abstract

The mobility of atoms, and cyclic or spherical guest molecules inside and around β -cyclodextrin 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 cyclodextrin, 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 previous work we proposed an analytical model for the interaction energy between α -, β - and γ -cyclodextrin with guest molecules of different structure and size [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 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 cyclodextrin (CD) and atoms, and cyclic or spherical guest molecules. The adsorption energy obtained from this model is only valid when the guest 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 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 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

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3 by the guest molecule with CD. However, the van der Waals term is the main
4 contribution to the total energy, particularly inside the cavity and so directly, determines
5 the configuration of the inclusion complex. To take into account the effects of the
6 solvent, other interaction energies must be applied.
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12 We also examine the influence of temperature on inclusion complex formation
13 by means of molecular dynamics (MD), since this simulation method is based on the
14 resolution of classical equations of motion to determine the trajectories of the particles
15 depending on the initial conditions [4-6]. By treating the results generated in this
16 process with statistical methods, one can obtain more detailed information about the
17 potential parameters related to the size and composition of the guest molecule that
18 influence formation of inclusion complexes with β -CD. In section 2 we present the
19 theoretical methods and in section 3, their main results.
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34 2. The Model

35 2.1. Expression of the interaction potential

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44 The intermolecular energy is modelled by a Lennard-Jones potential, which
45 represents the attractive and repulsive interactions between all atoms and molecules in
46 the system, even totally neutral ones. The essential effects of the confinement should be
47 preserved if we make the assumption of a continuum description of the cavity walls [1-
48 3], therefore the interaction energy W can be calculated as:
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$$55 W(\vec{r}_{mol}) = \rho_{CD} \int_S V(\vec{r}_{mol}, \vec{r}) d\vec{r} \quad (1)$$

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3 where the guest molecule-CD interaction is represented by an average over the
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5 uniformly distributed atoms in the CD. ρ_{CD} is the superficial density of atoms in the
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7 CD cavity, \vec{r}_{mol} is the position of the centre of mass for the guest molecule and $d\vec{r}$ is the
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9 differential element of the surface (on the cavity) located at \vec{r} . The CD is considered as
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11 a truncated cone, h being the axial length ($h \approx 7 \text{ \AA}$), b the radius of the larger base of the
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13 cone ($b \approx 5 \text{ \AA}$ for β -CD) and a the radius of the smaller top ($a \approx 4 \text{ \AA}$ for β -CD) [7].
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15 Here the Z axis is collinear with the cone axis (thus the XY plane is parallel to the cone
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17 base), and the origin of the coordinates lies at the centre of the cavity. When we
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19 consider the interaction energy W by the integration in Eq. (1), we are substituting the
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21 discrete atoms of the CD by a uniform distribution of mass on the cavity surface.
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23 Therefore, we can also replace the potential parameters for the different atoms
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25 belonging to the molecule $(\sigma_i, \varepsilon_i)$ and β -CD $(\sigma_j, \varepsilon_j)$ by some representative values for
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27 the composition of both systems. In order to bring out more clearly the dependence of
28
29 W on the composition of the guest molecule, we do not consider the values of these
30
31 parameters for β -CD and the guest separately, but represent the Lennard-Jones
32
33 parameters for the interaction between the atoms of the CD and the molecule by σ and
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35 ε . As we are dealing with a conical continuum geometry, for every plane $Z = \text{constant}$,
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37 the potential energy is the same for points (x_0, y_0) located at the same distance d from
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39 the cavity axis ($x_0^2 + y_0^2 = d^2$), for this reason we characterize the guest centre of mass
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41 position by the distance d from the cavity axis and the Z coordinate.
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53 The potential energy is determined by Eq. (1) for different positions of the guest
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55 centre of mass \vec{r}_{mol} , inside and outside the CD. In each plane $Z = \text{constant}$, about 500
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57 points are explored and the range of variation along the Z axis is about 10 \AA . The results
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59 obtained are represented by the potential energy surfaces, penetration potentials and the
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3 inclusion complex configuration, as in previous works [1-3]. The curve joining the
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5 minimum potential energy for every plane $Z = \text{constant}$ defines the penetration
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7 potential, which describes the variation in interaction energy when its path through the
8
9 cavity is non-axial. The position of the guest molecule for which we obtain the absolute
10
11 minimum potential energy gives the geometry of the inclusion complex.
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15 The potential energy surfaces are represented by partitioning the variation range
16
17 of the Z axis in the β -CD cavity into four parts, depending on the position of the guest
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19 molecule centre of mass near the top of the cone (region I), near the centre of the cavity
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21 (regions II and III) and near the cone base (region IV). The length of each domain is
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23 about 2 Å and the potential surface for each region is determined as the minimum
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25 energy for every point on the plane in the corresponding interval of Z .
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32 2.2. Simulation method

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36 Molecular dynamics (MD) is based on the resolution of classical equations of
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38 motion to determine the trajectories of the particles, depending on the initial conditions.
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40 The initial conditions of the guest molecule are in this case determined by the centre of
41
42 mass position and velocity. The magnitude of the initial velocity depends on the
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44 temperature of the process, but its direction in each trajectory and the initial centre of
45
46 mass position are determined randomly. The simulation time for each trajectory is 1 ns
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48 with a step of 1 fs and the configuration and energies (kinetic and potential) were
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50 written every 100 steps. We use an in-house program written in Fortran and the
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52 equations of motion to perform constant temperature molecular dynamics are integrated
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54 numerically using a variant of the leap-frog scheme (proposed by Brown and Clarke)
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56 [8], constraining the rotational and translational kinetic energies separately [9].
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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 \AA 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 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 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 size and composition, 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

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3 \vec{r}_{mol} . In order to perform a comparative study we consider different values for the
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6 parameter σ to represent the interaction between β -CD and the guest, because ε only
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8 acts as a scaling factor on the potential energy W .
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11 Figure 1 exhibits the penetration potential (solid curves) for guest molecules
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13 with different size and composition. It clearly resembles a well potential, deepening as
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15 the atomic or molecular size of the guest increases, and with small differences in the Z
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17 coordinate (near the cavity centre) of the minimum values W_{min} . This behaviour is
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19 similar to the well potential for the interaction between a guest molecule and CD,
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21 obtained by the sum of pairwise-additive potentials (as in molecular mechanics
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23 calculations) [13], and it means that guest molecule positions inside the cavity are more
24
25 stable than outside the β -CD. Figure 1 also exhibits the interaction energy along the
26
27 cavity axis (dashed curves). The two curves are seen to agree for molecules with
28
29 $\sigma = 4.1 \text{ \AA}$, as the size of the guest decreases there are some small differences in the
30
31 energy values near the larger base of the β -CD, and for small guest molecules the
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33 penetration potential is very different from the energy on the axis because in this case
34
35 the most stable molecular positions are located near the cavity walls. There are also
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37 greater differences in the values of W on the potential surface as the guest increases.
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45 The centre of mass position at the minimum energy W_{min} is determined by
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47 (d_{min}, z_{min}) (Table 1) and it can be seen that the distance between this position and the
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49 cavity axis d_{min} depends on parameter σ by $D_{min} = 1.12\sigma$, $D_{min} = u(z_{min}) - d_{min}$ being
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51 the distance between the cavity walls and the molecule in the more stable configuration
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53 and $u(z_{min})$ being the cone radius at the z_{min} coordinate, as occurs in the continuum
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55 model for the interaction between a linear molecule and β -CD [2, 3]. Therefore, the part
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57 played by the potential parameters in the interaction energy W is similar to that in the
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3 Lennard-Jones potential between a pair of atoms: ε governs the strength of the
4 interaction and σ is related to the position of the minimum energy ($r_{\min} = 1.12\sigma$) [14].
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8 The σ parameters selected in this work are of the same order of magnitude as pairs of
9 atoms like C-C, C-O, O-O, etc. and the minimum interaction energy between them at
10 the equilibrium position is $-\varepsilon$ (about -0.008 eV for such pairs) [14]. If we consider
11 this ε value for the interaction between cyclic or spherical molecules and the cavity, the
12 minimum energy W_{\min} ranges from -4.3 eV for $\sigma = 2.4$ Å to -22.8 eV for $\sigma = 4.1$ Å,
13 therefore the confinement in β -CD involves a more intense interaction, greater even
14 than for linear molecules [2, 3]. For instance, if we apply the present model to
15 cyclopentadiene, taking into account the results obtained by a force field method [13], it
16 can be represented by the parameters $\sigma = 3.5$ Å and $\varepsilon = 0.0004$ eV, ε being 5 times
17 less than for linear molecules such as acrylonitrile or methyl vinyl ketone. In Table 1
18 some samples of atoms and molecules are included along with some parameters that
19 simulate the interaction between β -CD with these guest molecules [13, 15, 16].
20
21 However, the interaction energies presented in this Table are obtained with $\varepsilon = 0.006$
22 eV, since ε only acts as a scaling factor on the potential energy W , these bindings
23 energies are about 10 times bigger than the values corresponding to real cyclic or
24 spherical molecules.
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47 Figure 2 shows the potential energy surfaces for atoms, cyclic or spherical
48 molecules with $\sigma = 2.8$ Å, $\varepsilon = 0.006$ eV (Fig. 2a) and for $\sigma = 3.7$ Å, $\varepsilon = 0.006$ eV
49 (Fig. 2b). They are similar in the size of the regions where the energy is attractive, this
50 feature being a consequence of the cavity geometry. The main differences in the
51 potential energy surfaces are related to the magnitude of the energy, which is largely
52 dependent on the molecular composition rather than its geometry, as occurs in the
53 continuum model for the interaction between a linear molecule and β -CD.
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3 Comparing the intermolecular potential presented in this study with the results
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5 obtained by the all-atoms model, the main discrepancies derive from the position of the
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7 guest centre of mass in the configuration of the inclusion complex, because this
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9 continuum model is only able to reproduce the position in the plane $Z = \text{constant}$ by the
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11 distance from the cavity axis instead of the (X, Y) coordinates.
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15 16 17 *3.2. Molecular Dynamics* 18 19 20 21

22 The evolution of the guest molecule in each trajectory and the resultant average
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24 energy are different because the initial conditions determine the integration of the
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26 equations of motion. The initial velocity does not influence the number densities and the
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28 mean energy of the process, but the starting centre of mass position determines the
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30 behaviour of the guest in each process and decisively affects the probability of forming
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32 inclusion complex. When the guest initial position is located outside the cavity walls the
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34 molecule always stays on the outside of the β -CD where it does not reach a stable
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36 configuration, moving around the cavity continually or even tending to move away.
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38 During trajectories whose starting molecular configuration is near the rims of the β -CD
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40 the guest tends to enter the cavity, remain inside forming an inclusion complex or exit
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42 from it after a period, depending on the potential parameters. However, inside the cavity
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44 the molecule does not reach a stable configuration because it is fluctuating around the
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46 most probable position \vec{r}_p with an amplitude that also depends on parameters (σ, ε) .
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48 This effect can be appreciated in Figure 3, which shows the position probability for
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50 molecules with different σ and the same ε , and includes a schematic representation of
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52 the projections of the cavity in the plane. The range of oscillations inside the β -CD
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54 increases as the molecular size decreases, which means greater delocalization for the
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3 guest and thus smaller values for the position probability. The maximum probability
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6 P_{\max} and the corresponding position of the guest $\vec{r}_p = (d_p, z_p)$ are presented in Table 2.
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9 It can be seen that the most probable configuration ranges from near the cavity walls to
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11 the centre of the β -CD as the molecular size increases: so taking into account the
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13 method used to calculate the position probability density, we conclude that it
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15 corresponds to the minimum energy configuration of the complex in this type of
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17 molecule. The mean energy for the simulation W_{mean} of different molecules is also
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19 presented in Table 2. W_{mean} is greater than W_{min} because the energy of every position
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21 with probability different to zero contributes to the average energy, for bigger molecules
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23 there are greater energy differences inside the β -CD and so greater differences from
24
25 W_{min} (Fig. 4). In order to analyse the dependence of the results on the length of the
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27 simulation, Figure 4 shows the variations of the potential energy during a trajectory for
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29 different guest molecules. There are no great differences between the mean values for 1
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31 and 2 ns (about 4 parts in 1000), however the computer time needed for carrying out the
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33 simulation is considerably shorter. If we compare the position probability density for
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35 these simulation times, we conclude that the most probable positions are the same and
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37 the distribution is similar for each case. But for 2 ns we obtain greater values for the
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39 position probability, implying therefore more stabilization of the system and similar
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41 results to 1 ns. We can conclude that a simulation time of 1ns is adequate for this
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43 system.
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52 For molecules with $\sigma \geq 3.0 \text{ \AA}$, the parameter ε only acts as a scaling factor in
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54 W_{mean} and does not influence the position probability density. For molecules with
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56 $\sigma < 3.0 \text{ \AA}$, ε affects the amplitude of oscillations around the most probable position: a
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58 greater value of the parameter implies smaller fluctuations (Fig. 5). The meaning of ε
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3 as strength of the interaction is also reflected in the dynamic behaviour of the system,
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5 because while the guest with $\sigma = 2.8 \text{ \AA}$ and $\varepsilon = 0.006 \text{ eV}$ remains inside the cavity for
6
7 the whole simulation time, for $\varepsilon = 0.003 \text{ eV}$ the molecule only spends a period
8
9 (inclusion time t) inside, after which it exits from the CD and moves away. This t
10
11 depends on the initial conditions and decreases as temperature increases (the mean
12
13 inclusion time is 394 ps at 293 K, 381 ps at 323 K and 356 ps at 363 K).
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16
17 The probability of forming inclusion complex P_{inc} is presented in Table 2. The
18
19 differences in P_{inc} are due mainly to the distance from the rims of the β -CD at which
20
21 each molecule must be located initially to enter the cavity, although in some cases the
22
23 guest exits from the host after the inclusion time. This distance is usually further from
24
25 the wide end of the β -CD, and ranges from 3 \AA for $\sigma = 2.4 \text{ \AA}$ to 6 \AA for $\sigma = 4.1 \text{ \AA}$.
26
27 Therefore, considering the same grid around the cavity in all cases, we can conclude
28
29 that larger molecules have greater probabilities of forming inclusion complexes. P_{inc} is
30
31 independent of parameter ε but the temperature T of the process influences P_{inc}
32
33 decisively, because the magnitude of the initial velocities depends on T and determines
34
35 the maximum distance from the rims needed by the molecule to enter the cavity. These
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37 values for $T = 323 \text{ K}$ are approximately double those for $T = 293 \text{ K}$, this means that
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39 P_{inc} increases as T does although the ratio between the probabilities of different-sized
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41 molecules remains similar.
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50 The suitability of the model presented in this work can be confirmed by
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52 comparing results with those of Ref. 10 and 11, where Lipkowitz et al. studied where
53
54 and how different analytes bind to permethylated β -CD in gas chromatography using
55
56 different computational methods (standard molecular dynamics and Monte Carlo
57
58 simulations). The structure of some considered selectands is essentially cyclic and in the
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3 case of pinene, the intermolecular forces responsible for holding the host-guest complex
4 are exclusively van der Waals forces [17]. They conclude that the preferred binding site
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7 for small analytes is the interior of the macrocycle with rapid shuttling between the
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10 primary and secondary rims of the host cavity, in accordance with the results obtained
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13 by the model presented in this study.

14 15 16 17 18 **4. Conclusions**

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23 We have studied the mobility of atoms, cyclic or spherical guest molecules
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25 inside and around β -CD by molecular dynamics simulation at constant temperature.
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27 The intermolecular energy is modelled by a Lennard-Jones potential and a continuum
28
29 description of the cavity walls. It is found that the variation of the potential energy
30
31 along the Z coordinate (parallel to the cavity axis), resembles a well potential where the
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33 minimum energy is lower as the atomic size of the molecule increases. The distance
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35 between the cavity walls and the guest molecule in the absolute minimum energy
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37 configuration is approximately 1.12σ and ε governs the strength of the interaction.
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43 In the dynamical study of the system we can conclude that the molecule can
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45 enter the cavity and then form an inclusion complex only for certain initial positions of
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47 its centre of mass, and these positions are always near the rims of the CD and never
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49 outside the cavity walls. The probability of forming an inclusion complex increases with
50
51 the size of the guest molecule and the temperature of the process. The most probable
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53 configuration of the complex formed with cyclic or spherical molecules corresponds to
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55 that of minimum energy. The temperature of the simulation affects the inclusion time
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57 spent by the guest inside the cavity, when its interaction with β -CD is represented by
58
59 parameters $\sigma < 3.0 \text{ \AA}$ and $\varepsilon \leq 0.003 \text{ eV}$.
60

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TABLES

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

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

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 inclusion complex P_{inc} for the simulation of molecules with $\varepsilon = 0.006$ eV at 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

Figure Captions

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

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

Fig. 3: Projections on the XY and XZ plane of the probability density of presence for guest molecules with different σ , $\varepsilon = 0.006$ 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.

Fig. 4: The potential energy during a trajectory for guest molecules with different σ and $\varepsilon = 0.006$ eV.

Fig. 5: Projections on the XY and XZ plane of the probability density of presence for guest molecules with different ε , $\sigma = 2.8$ 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.

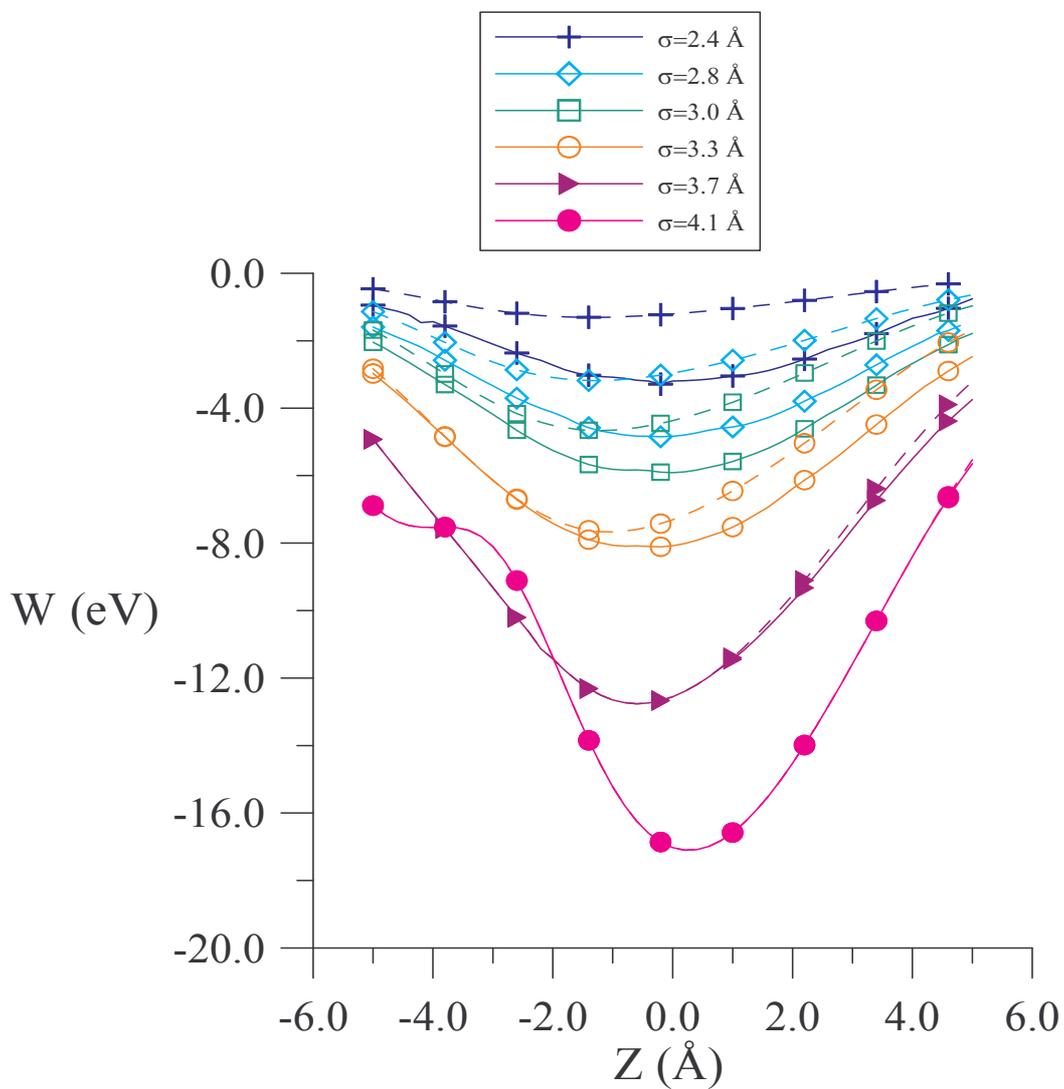


Figure 1

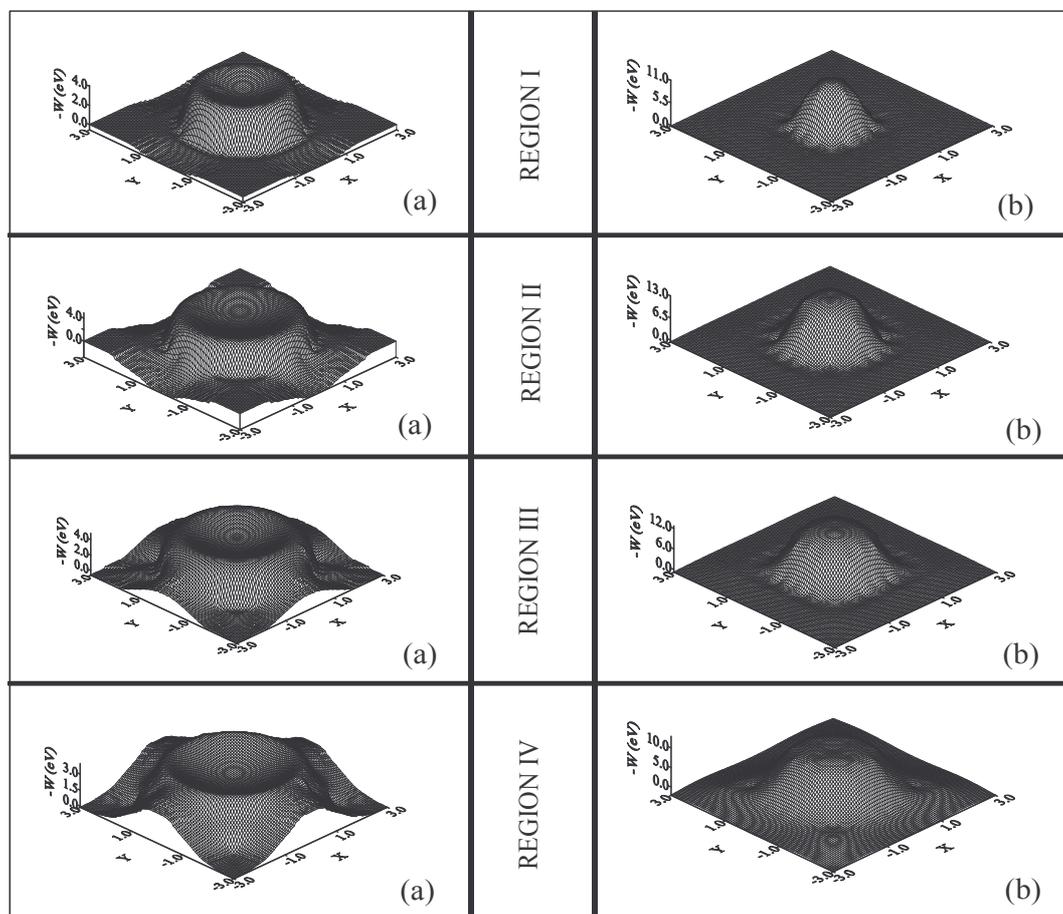


Figure 2

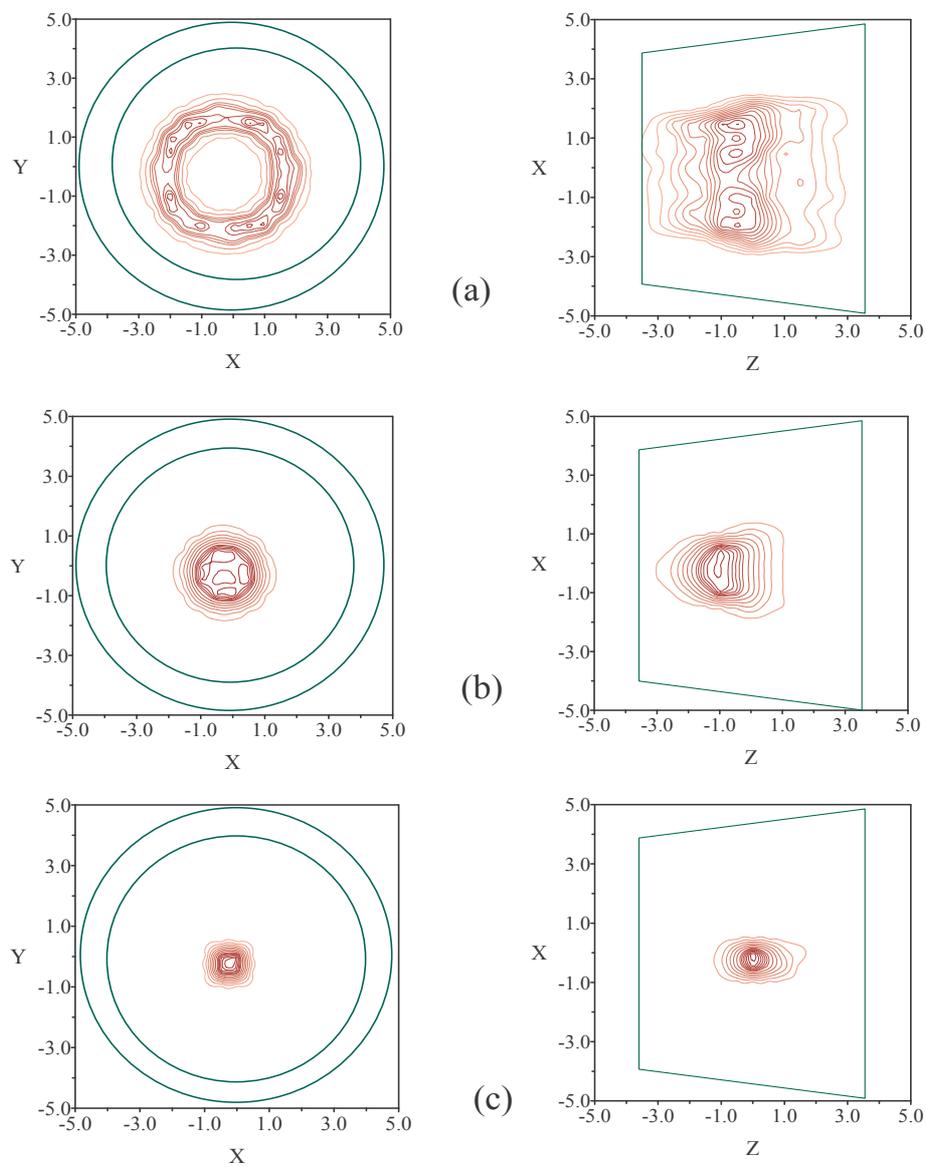


Figure 3

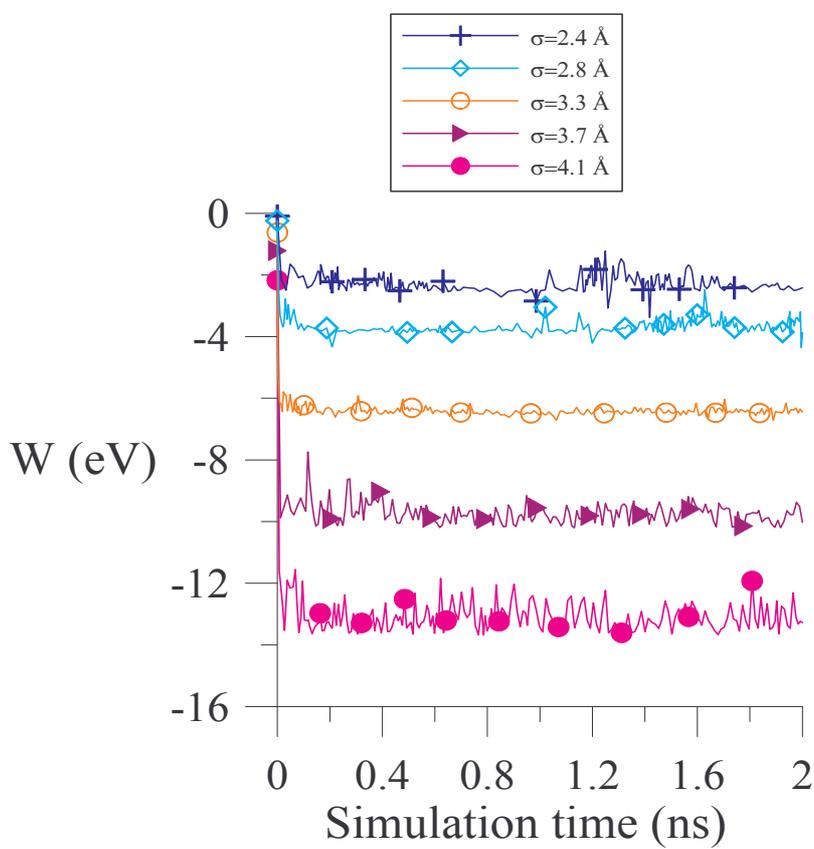


Figure 4

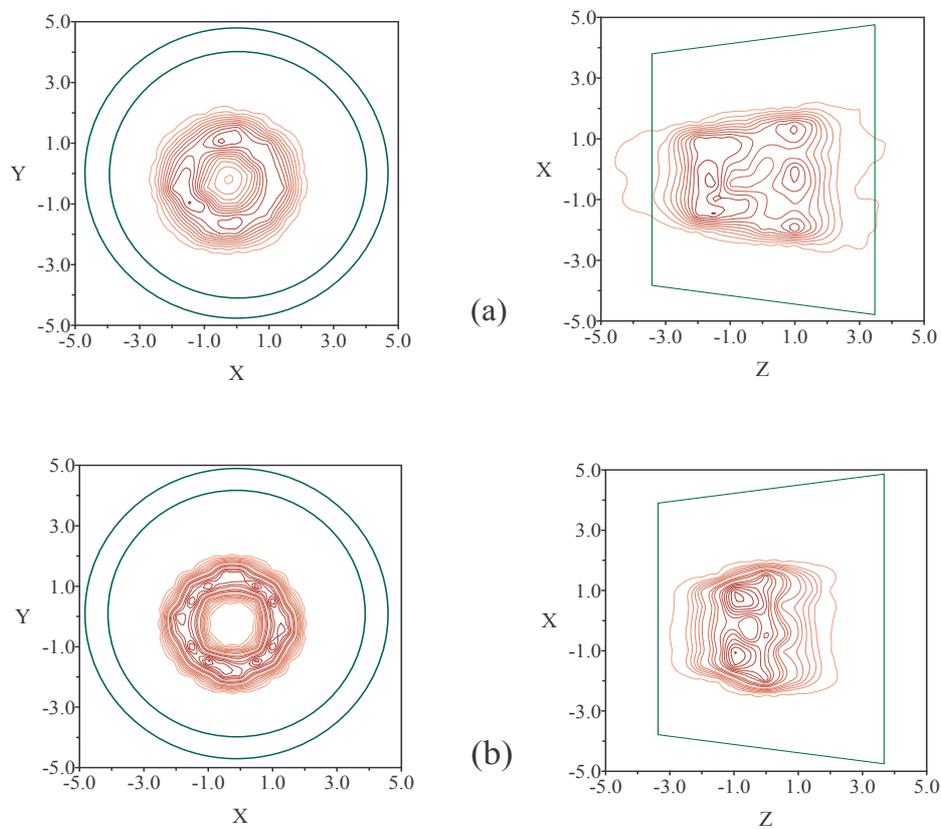


Figure 5