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**MOBILITY OF LINEAR MOLECULES INSIDE AND
AROUND β -CYCLODEXTRIN**

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Abstract

To analyse the mobility of linear guest molecules inside and around β -cyclodextrin, as well as their capacity to form inclusion complexes, a molecular dynamics simulation was carried out at constant temperature. Molecules with length $L < 5 \text{ \AA}$ can form inclusion and non-inclusion complexes, depending on the composition and initial position of the guest with respect to the cavity. Linear molecules whose interaction with β -cyclodextrin is represented by one pair of values for the Lennard-Jones parameters (σ, ε) and length $L \geq 5 \text{ \AA}$ can travel inside and outside the cavity, they can even pass through the cyclodextrin forming temporarily inclusion complexes. This inclusion time increases with the molecular length and decreases with the temperature of the simulation.

Keywords: inclusion complex, macromolecule, computer simulation, molecular mechanics, molecular dynamics.

1. Introduction

Cyclodextrins (CDs) are macrocyclic molecules composed of glucose units (7 in β -CD) forming truncated cone-shaped compounds. Their capacity for catalysis and chiral recognition is due mainly to the formation of inclusion complexes when some lipophilic part of a molecule enters the hydrophobic cyclodextrin cavity [1]. Until recently it was thought that all complexes with CDs were inclusion complexes. However, experimental studies by several research groups show the possibility of forming both inclusion and non-inclusion complexes with CDs [2]. Specifically in pharmaceutical drug delivery, there is growing evidence that supports the important contribution of non-inclusion-based phenomena for drug solubilization by cyclodextrins, including surfactant-like effects and molecular aggregation [3]. Non-inclusion complexes are also important in gas chromatography, where chiral recognition can take place on the exterior of the CD because one of the predominant forces (the hydrophobic force) for host-guest complexation in aqueous phase liquid chromatography is absent in this case [2, 4]. The aim of the present work was to determine the conditions in which a linear molecule can form an inclusion or non-inclusion complex with β -CD.

A simulation method attempts to relate the microscopic details of a system to macroscopic properties of experimental interest. The first step in performing a molecular simulation requires knowledge of the potential energy of interaction between the particles of the system [5-7]. In previous work to simulate the interaction energy between β -CD and linear molecules, a model was constructed from a simple pairwise-additive Lennard-Jones potential combined with a continuum description of the cyclodextrin cavity and the guest molecule [8-10]. This model reproduces the main

energetic and structural features of the physisorption, in particular that guest molecule positions inside the cavity are more stable than outside the CD, as amply confirmed by molecular mechanics calculations (MM) [4]. Therefore this model cannot explain the existence of non-inclusion complexes, and this is not a consequence of model assumptions such as rigidity of molecules or ignoring the effects of solvent. Neither does this model allow the effect of temperature to be included in the process. The aim of the present work is to analyse the mobility of the guest molecule inside and around the β -CD, and the influence of temperature on inclusion complex formation. It was carried out by molecular dynamics (MD), because 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. By treating the results generated in this process with statistical methods, one can obtain more detailed information about the structural factors of the linear molecule (length and composition) that influence the inclusion complex formation with β -CD. In section 2 we present the theoretical methods and their main results in section 3.

2. Simulation Method

From the model published for the interaction energy between a linear molecule and β -CD, we consider rigid non-polar guest molecules [9, 10]. 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. Since continuity is assumed for the guest and the cavity, this interaction energy is not capable of reproducing the hydrogen bonds formed by the linear molecule

with CD. We do not consider the potential parameters for β -CD and the guest separately, but the interaction between the atoms is represented by one pair of values for the Lennard-Jones parameters (σ, ε) , where ε governs the strength of the interaction and σ defines a scale of length. In a forthcoming article we will consider the interaction between the atoms of the system composed of two different parameters pairs $(\sigma_1, \varepsilon_1; \sigma_2, \varepsilon_2)$, as in the continuum model [10].

We place the origin of the reference system at the centre of mass of the CD and the space-fixed frame over the principal axis of the β -CD. The configuration of the linear guest is given by the coordinates of its centre of mass and molecular orientation, which is defined by the polar angles (θ, φ) formed with respect to the absolute frame (X, Y, Z) . In rigid-body dynamics the molecular motion can be decomposed into two completely independent parts, translational motion of the centre of mass and rotation about the centre of mass. A basic result of classical mechanics is that the former is governed by the total force acting on the body, whereas the latter depends on the total applied torque. For a linear molecule, the angular velocity and the torque must be perpendicular to the molecular axis at all times [6, 7].

To integrate the equations of motion it is necessary to establish the initial conditions of the guest molecule: centre of mass position, orientation and velocities (translational and rotational). The magnitude of the initial velocities depends on the temperature of the process, but the direction of the translational velocity in each trajectory and the initial centre of mass position are determined randomly. We have calculated 9 trajectories that correspond to different initial configurations of the guest with respect to the β -CD: near the primary (narrow end) and secondary rims (wide end) of the CD, and outside the cavity walls (3 trajectories in each case). This way all of the important regions in and around the CD are sampling, and the multiple interactions an

analyte molecule experiences through a chromatographic column can be emulated. The simulation time for each process is 1 ns with a step of 1 or 10 fs (according to the molecular length) and the configuration and energies (kinetic and potential) were written every 100 steps. We used an in-house program written in Fortran [11] and the equations of motion to perform constant temperature molecular dynamics were integrated numerically using a variant of the leap-frog scheme (proposed by Brown and Clarke) [12], constraining the rotational and translational kinetic energies separately [13].

To determine the preferential binding site and orientation of the guest molecule, the number densities of presence in a volume element were calculated. We defined 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 [11, 14, 15]. 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. The most probable orientation is that with greatest number density.

The simulation was carried out for linear molecules with different length and composition, and at different temperatures.

3. Results and discussion

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. However, they affect the simulation in a different way: while the

molecular orientation and velocities hardly influence the number densities and the mean energy of the process, the greatest differences in these values are due to the initial position of the guest centre of mass, which also determines the behaviour of the guest in each process because it can give rise to stable or unstable configurations. In some cases the molecule moves for several ps in the trajectory until it reaches a stable configuration in which it remains for the longest period in the simulation. The complex was considered stabilized when the difference between the angles or centre of mass coordinates in two consecutive positions was lower than 0.001° and $0.01 \text{ \AA}$ respectively. In all cases, we observed when the initial centre of mass position was located outside the cavity walls, the molecule always stayed on the outside of the CD where it does not reach a stable configuration, moving around the cavity continually or even tending to move away.

The results depend on the length L of the linear molecule but the molecular evolution is similar for $L < 5 \text{ \AA}$ and different for lengths $L \geq 5 \text{ \AA}$, so we can analyse the mobility of the guest for each category:

a) On comparing the evolution of a linear molecule with length $L < 5 \text{ \AA}$ characterized by parameters (σ, ε_1) and another with (σ, ε_2) , different trajectories that always lead to the same results were found: the parameter ε did not affect the resulting position probability density and acts as a scaling factor on the average energy. Therefore the simulation was performed assuming the interaction between β -CD and guest molecule to be represented by the potential parameter σ , as in the continuum model [9]. There were two different types of behaviour, depending on the molecular composition, and then two categories characterized by the potential parameter σ : $\sigma < 3.5 \text{ \AA}$ and $\sigma \geq 3.5 \text{ \AA}$.

— $\sigma < 3.5 \text{ \AA}$. The mean energy in each trajectory for $L = 4.5 \text{ \AA}$, $\sigma = 3 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$ at temperature $T = 293 \text{ K}$ is detailed in Table 1 and the probability density of presence is shown in Figure 1a, where a schematic representation of the projections of the cavity and the guest in the plane has been inserted. When the starting positions of the guest are near the primary (processes P1, P2, P3) and secondary rims (P4, P5, P6) of the β -CD, the linear molecule tends to move towards and remain inside it, forming a stable complex. The greatest probability of presence (about 62%) corresponds to inner positions of the guest centre of mass at $1.5 \text{ \AA}$ from the wide end of the CD, forming an angle $\theta \approx 90^\circ$ with the cavity axis (Fig. 1a). This is an inclusion complex but with a different configuration than that of minimum energy, in which the guest is located near the CD centre of mass with $\theta \approx 24^\circ$ and whose energy is -10.05 kcal/mol [9]. As the σ parameter increases, the guest tends to position itself nearer the wide end of the β -CD. The probability of presence on the exterior of the β -CD (trajectories P7, P8 and P9) is about 13% and the mean energy is higher than inside the β -CD (Table 1).

— $\sigma \geq 3.5 \text{ \AA}$. In this case the linear molecule cannot penetrate into the cavity and always remains outside the β -CD, where it can form stable non-inclusion complexes. The average energy in each trajectory for $L = 4.5 \text{ \AA}$, $\sigma = 4 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$, $T = 293 \text{ K}$ is shown in Table 1 and the probability density of presence in Figure 1b. During the processes P1, P2 or P3, the guest stays near the narrow end of the CD, forming an angle of about 90° with the cavity axis and the mean energy is higher than the trajectories P4, P5 or P6, where the most stable position is external and parallel to the wide rim of the β -CD. In this case, the guest has the same probability of forming the two complexes (about 30%) because we have considered the same number of trajectories starting from each rim of the CD.

This calculation was also carried out at temperatures $T = 323$ and 363 K and we conclude that, although the stabilization time increases with temperature, it does not affect the mean energy of the simulation or the position probability density for molecules with $L < 5$ Å.

b) For linear molecules with length $L \geq 5$ Å the molecular evolution is similar for every value of parameter σ . During trajectories P1, ..., P6, the guest tends to move towards the cavity, remain inside it (forming an inclusion complex) and exit from the CD (Fig. 2) where the linear molecule can reach a stable configuration, or even tend to move away. However, the guest does not pass through the cavity as in Figure 2 in every process, it can enter and exit from the same rim of the CD during the trajectory. The time spent inside the cavity (inclusion time t) varies from several to a hundred ps and depends on the length and composition of the guest, the temperature and initial conditions of the trajectory. Molecular dynamics calculations performed on complexes of phenol and benzoic derivatives with α -CD also suggest the guest possibly moves in and out the host on a 10-100 ps scale [16].

The inclusion time t during trajectories P1, ..., P6 for $L = 7$ Å, $\sigma = 3$ Å, $\varepsilon = 0.07$ kcal/mol at temperature $T = 293$ K is presented in Table 1, where the values for processes P7, P8 and P9 have not been included because when the initial centre of mass position was outside the cavity walls the molecule always stayed outside the CD. As can be seen, the time t is negligible compared to the simulation time (1 ns) and therefore does not influence the probability of presence, whose greatest value corresponds to positions of the guest near the cavity walls (about 8.6 %) (Fig. 3a). However the linear molecule does not reach a stable configuration there, on the contrary the most probable external configuration (about 7.3 %) has the guest centre of mass at 1.5 Å from the wide rim of the CD, with $\theta \approx 77^\circ$ (Fig. 3a). If we consider the length of time in trajectories

P1, ..., P6 as the corresponding inclusion time, the greatest probability of presence (about 20%) corresponds to outer positions of the guest centre of mass at $0.5 \text{ \AA}$ from the wide end of the CD, forming an angle $\theta \approx 64^\circ$ with the cavity axis (Fig. 3b), although there is another possible position near the narrow rim (about 15%).

The average energy over the simulation time for $L = 7 \text{ \AA}$, $\sigma = 3 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$ at temperature $T = 293 \text{ K}$ is presented in Table 1. In this case, the mean energies of trajectories P7, P8 and P9 are the lowest because during these processes the linear molecule is usually rotating and moving around near the cavity walls, whereas during trajectories P1, ..., P6 for most of the simulation time the guest reaches less stable external configurations than inside the cavity or near its walls. The average energy over the simulation time becomes lower for linear molecules with $L \geq 5 \text{ \AA}$ and the same composition as the molecular length increases (i. e. -4.3 kcal/mol for $L = 9 \text{ \AA}$, $\sigma = 3 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$), although always higher than $L = 4.5 \text{ \AA}$ because those molecules tend to remain outside the cavity for most of the simulation time. The average energy over the inclusion time for a linear molecule with $L = 7 \text{ \AA}$, $\sigma = 3 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$ at temperature $T = 293 \text{ K}$ is also presented in Table 1. There is no proportional relation between the inclusion time and the mean energy of the trajectory, lower interaction energies correspond to when a larger part of the linear molecule is inside the cavity. This is also the reason for the wide differences between the mean energies of the processes. On comparing the average energy during the inclusion time for $L = 7$ and $4.5 \text{ \AA}$, it can be concluded that the β -CD inclusion complexes formed with linear molecules of these lengths and the same composition yield lower average energies as the molecular length increases, in agreement with MM calculations. The influence of molecular relaxation on the interaction energy between β -CD and the guest is widely confirmed in molecular mechanics calculations [2, 4]. However, many

theoretical studies carried out by rigid-body molecular dynamics have produced accurate results in accordance with experiments, depending on the simulation period [17]. Time is therefore a decisive factor.

The inclusion time t depends on the initial conditions of the trajectory, therefore to study its dependence on the temperature T of the process, linear molecule length L and the composition represented by the potential parameters σ and ε , we considered the same initial conditions for the trajectories P1, ..., P6 of every molecule. The influence of parameter ε on time t is negligible against that of the other parameters, it contributes mainly to the magnitude of the mean energy. The average inclusion time for a molecule with length L and parameter σ varies less than 10% for a threefold ε , these variations are not enough to change the shape of Figure 4a. This figure represents the average inclusion time for processes P1, ..., P6 against the σ of different length linear molecules. The following features can be pointed out:

- i) For a linear molecule with length L , the inclusion time t grows with σ (size of the atoms) until it reaches a maximum of $\sigma_{\max}$, after which it decreases.
- ii) The inclusion time t for linear molecules with the same composition (represented by σ) increases with L .
- iii) The value of $\sigma_{\max}$ decreases when L increases.

Figure 4b represents the mean energy during the inclusion time t of processes P1, ..., P6 for the same linear molecules as Figure 4a. In order to clarify the effect of confinement inside the cavity on the average energy, we use the same value of ε . The following main features stand out:

- i) Lower interaction energies correspond to a greater σ (size of atoms), although the relationship between them is not a straight line.

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- ii) The average energy for molecules with $\sigma \leq 2.7 \text{ \AA}$ and length $L = 7 \text{ \AA}$ is the same as $L = 8 \text{ \AA}$ and higher than for $L = 9$ and $L = 10 \text{ \AA}$. This means that the stability of β -CD inclusion complexes formed by molecules with compositions characterized by $\sigma \leq 2.7 \text{ \AA}$ increases as the molecular length does.
- iii) The average energy for linear molecules with different lengths and the same composition is nearly the same when $\sigma \geq 2.7 \text{ \AA}$. Thus, for molecules with length $L > 7 \text{ \AA}$, only the inner part of the guest inside the cavity contributes significantly to the interaction energy, its maximum value being equal to the axial length of the CD (about $7 \text{ \AA}$).

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Figure 4c represents the average inclusion time for processes P1, ..., P6 against the temperature T of the simulation, for linear molecules with different length and composition (we use the same value of ε). The time spent by the guest inside the cavity t is seen to decrease as temperature rises, the differences being smaller when σ is greater. There is no relationship between the length of the molecule and the variations in inclusion time t with temperature T , which can be about 0.4 ps . Although this seems a negligible amount, for molecules with $L = 10 \text{ \AA}$, $\sigma = 2.7 \text{ \AA}$ and retention time of 20 min , it means a decrease of about 2 min when temperature increases. The mean energy over the inclusion period for a linear molecule (with parameters L , σ and ε) does not depend on the temperature because again only that part of the guest located inside the cavity contributes to the interaction energy, independently of the time spent there.

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The dynamics simulation program used in this work was previously employed to investigate the enantioselectivity of equol in β -CD [11]. One of the results obtained in that study was that the guest remained inside the cavity for most of the simulation time, in agreement with experimental findings. The discrepancy with the results of the present

work is due to the differences in potential energy, because the van der Waals contribution to the interaction energy between the chiral host and each enantiomer [18] is not in accordance with the continuum model of physisorption energy for those linear molecules whose interaction with β -cyclodextrin is represented by one pair of values for the Lennard-Jones parameters (σ, ε) and length $L \geq 5 \text{ \AA}$ [9] (applied in the present study).

4. Conclusions

We have studied the factors influencing the evolution of a linear molecule interacting with β -CD, using molecular dynamics simulation at constant temperature. In this work we have considered molecules whose interaction with β -CD is represented by one pair of values for the Lennard-Jones parameters (σ, ε) . We conclude that the molecules with length $L < 5 \text{ \AA}$ can form inclusion and non-inclusion complexes, depending on the composition and initial position of the guest with respect to the cavity. Linear molecules with length $L \geq 5 \text{ \AA}$ have a small probability of forming non-inclusion complexes, again depending on the composition and initial position of guest and cavity. They can form inclusion complexes for a time period which depends on the molecular properties (length and composition of the guest) as well as on the temperature and initial conditions of the trajectory. The inclusion time increases with the length of the guest and decreases with the temperature of the process. By comparing the average energy over the simulation and inclusion time for linear molecules with different lengths and compositions, it can be concluded that MD can produce precise results in accordance with experiment, depending on the simulation time. Time is therefore a decisive factor.

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TABLES

Table 1. The mean potential energy (in kcal/mol) for the simulation of linear molecules with $\varepsilon = 0.07$ kcal/mol at temperature $T = 293$ K.

Process	$L = 4.5 \text{ \AA}$		$L = 7 \text{ \AA}$	t (ps)	$\sigma = 3 \text{ \AA}$
	$\sigma = 3 \text{ \AA}$	$\sigma = 4 \text{ \AA}$			
	Mean energy (kcal/mol)	Mean energy (kcal/mol)	Mean energy (kcal/mol)		Mean energy (t) (kcal/mol)
P1	-6.26 ± 0.42	-5.28 ± 0.38	-3.49 ± 2.33	3.5	-10.05 ± 3.15
P2	-6.28 ± 0.37	-5.19 ± 0.34	-3.02 ± 0.85	1.9	-7.70 ± 2.95
P3	-6.32 ± 0.31	-5.14 ± 0.40	-3.52 ± 1.63	1.8	-7.36 ± 2.73
P4	-6.29 ± 0.29	-7.12 ± 0.35	-3.61 ± 0.72	4.3	-6.78 ± 1.95
P5	-6.24 ± 0.32	-7.16 ± 0.37	-2.89 ± 0.62	1.3	-6.14 ± 1.11
P6	-6.27 ± 0.39	-7.18 ± 0.43	-3.05 ± 0.41	1.1	-3.87 ± 1.10
P7	-3.70 ± 0.38	-5.51 ± 0.75	-5.57 ± 0.46	—	—
P8	-3.76 ± 0.29	-5.37 ± 0.83	-5.53 ± 0.42	—	—
P9	-2.59 ± 1.73	-5.16 ± 0.95	-5.63 ± 0.37	—	—

Figure Captions

Fig. 1: (a) Projections on the XY and XZ plane of the probability density of presence for linear molecules with $L = 4.5 \text{ \AA}$, $\sigma = 3 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$ at temperature $T = 293 \text{ K}$. A schematic representation of the projections of the cavity and the guest has been inserted in the figure.

(b) Same as (a) for linear molecules with $L = 4.5 \text{ \AA}$, $\sigma = 4 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$ at temperature $T = 293 \text{ K}$.

Fig. 2: The movements of a linear molecule with $L = 7 \text{ \AA}$, $\sigma = 3 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$ along the P1 trajectory at temperature $T = 293 \text{ K}$.

Fig. 3: (a) Projections on the XY and YZ plane of the probability density of presence over the simulation time for linear molecules with $L = 7 \text{ \AA}$, $\sigma = 3 \text{ \AA}$, $\varepsilon = 0.07 \text{ kcal/mol}$ at temperature $T = 293 \text{ K}$. A schematic representation of the projections of the cavity and the guest has been inserted in the figure.

(b) Same as (a) for the probability density of presence over the inclusion time.

Fig. 4: (a) The average inclusion time for processes P1, ..., P6 against the σ of different length linear molecules.

(b) The mean energy during the inclusion time t of processes P1, ..., P6 for the same linear molecules as Figure 4a.

(c) The average inclusion time for processes P1, ..., P6 against the temperature T of the simulation, for linear molecules with different length and composition.

Figure 1

Figure 2

Figure 3

Figure 4