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Note

A molecular modeling study on the interaction between β-cyclodextrin and synthetic pyretroids

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Abstract

The interaction between four cycloprothrin derivatives and β-cyclodextrin was investigated by means of molecular dynamics. Several in vacuo trajectories were calculated for each system imposing a 1:1 stoichiometry. Moreover, for one particular guest–host couple, the 1:2 guest–host ratio was investigated. We also took into account the influence of the solvent and of the temperature. The results account for the formation of adducts which are stable at room temperature. The formation of the adduct involves the phenyl groups of the guest molecules which mainly interact with the hydrophobic cavity of the host by van der Waals forces. © 1997 Elsevier Science Ltd.

Keywords: Cyclodextrin; Pyrethroid; Molecular dynamics; Inclusion complexes

1. Introduction

Cyclodextrins are a group of cyclic oligosaccharides with a ring structure which is basked-like shaped. These compounds are able to include several kinds of molecules into their internal cavity. The interaction with the cyclodextrin molecule leads to important modifications of the properties of the guest compound, allowing the fixation of volatile materials, the protection against oxidation and photolysis, modification of the reactivity and of the biological properties [1–4]. When applied to pesticides, the inclusion can modify their characteristics in various ways.

Pyrethrum is a natural insecticide whose safety and effectiveness are well known, but its instability in air and light limits its use in agriculture. Two strategies have been developed to overcome these difficulties: (a) the synthesis of more persistent pyrethroids and (b) the search for a more efficient application of the existing pyrethroids [5]. In recent years molecular modeling techniques (e.g., molecular dynamics and molecular mechanics) have been successfully applied to the study of the interactions between the β-cyclodextrin molecule and small ligand molecule [6–11].

In this study we present the results of a series of molecular dynamics (MD) experiments carried out on

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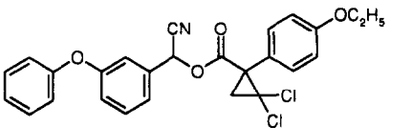
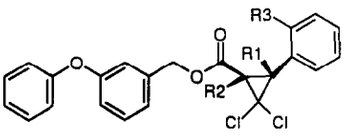
the inclusion complexes of the β-cyclodextrin (BCD) with four synthetic pyrethroids. The geometry of the complexes and the energy differences are computed. Moreover we investigated the influence of the temperature on the stability of the complexes, the effect of the solvent and the formation of complexes involving two BCD molecules.

2. Materials and methods

The prototype of the guest molecule is derived from the cycloprothrin (CYCLOSAL), a pyrethroid insecticide invented by the CSIRO (Australian Commonwealth Scientific and Industrial Research Organization) [12,13]; it is shown in Scheme 1 together with the four different guest molecules (P1–P4) employed in the simulations. These compounds were recently synthesized by one of us (G.D., unpublished results).



Cycloprothrin



Guest molecule

	R1	R2	R3
P1	H	H	H
P2	H	CH3	H
P3	H	H	OCH_3
P4	C_6H_5	H	H

Scheme 1.

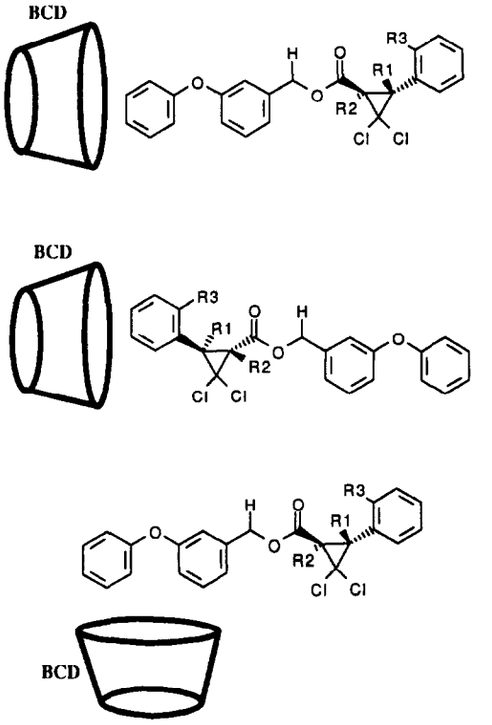
The prototype of the guest molecule is derived from the cycloprothrin (CYCLOSAL), a pyrethroid insecticide invented by the CSIRO (Australian Commonwealth Scientific and Industrial Research Organization) [12,13]; it is shown in Scheme 1 together with the four different guest molecules (P1–P4) employed in the simulations. These compounds were recently synthesized by one of us (G.D., unpublished results).

The β-cyclodextrin (BCD) molecule consists of seven D-glucopyranose monomers connected by α-(1 → 4) linkages. Topologically this molecule can be represented by a toroid in which the primary and secondary hydroxyl groups are placed on the smaller and the larger circumferences, respectively. No hydroxyl group is present within the toroid cavity which, accordingly, has a pronounced hydrophobic character.

The MD experiments were performed employing the DLPOLY2 program. [1] The structure of the BCD molecule was taken from the Cambridge Structural Database. The AMBER plus OLYCAM [14] force field was used with the adequate adaptations (e.g., the amber CT type carbon atom was employed for the sp3 carbon in P1–P4; and so on). The partial atomic charges were fitted to the electrostatic potential computed by ab initio GAMESS calculations performed at the 6-31G accuracy level on a fragment formed by 3 glucopyranose units. A relative dielectric constant value of 1.0 was employed in all the simulations Calculation were carried out on IBM RS6000 and HP9000 computers at the Department and CNR location.

For each of the four host–guest couples, for the BCD and for each of the guest molecules 9 in vacuo MD trajectories were generated. The docking of the guest to the host was made according to the topologies showed in Scheme 2.

The in vacuo MD runs were performed at $T = 298$ K, with no periodic condition applied, as we were concerned only in studying the docking of the guest molecule to the host; we also carried out on the



Scheme 2. Sketch of the different topologies for the entry of the guest molecule into the cavity of the BCD host.

[1] DLPOLY2 is a package of molecular simulation routines written by W. Smith and T.R. Forester, copyright the Council for the Central Laboratory of the Research Councils, Daresbury Laboratory, Nr Warrington (1994–1996).

BCD-P1 system a set of MD run at $T = 300$, 310, 320, 330, 340 and 350 K. The BCD_2-Pn complex formation was taken into consideration docking the guest Pn molecules between two BCD units. The MD simulations of the BCD-P1–water system were performed at constant volume and temperature in a cubic cell with 25 Å edges, the initial configuration was obtained by adding 200 water molecules to the BCD-P1 equilibrium configuration. The water addition was performed by means of a DLPOLY utility. Moreover, 4 water molecules were inserted into the BCD cavity.

Each trajectory was equilibrated for 500 ps with a time step of 0.001 ps. Then a 2500 ps run was performed collecting the trajectories data. The Average Configuration Energy (ACE) values were computed averaging the total (kinetic + potential) energy values over the 2500 ps run and then used to calculate the interaction energy values reported in Table 2. The MD runs performed on to the BCD_2-P1 and the BCD-P1–water adducts were stopped after 5000 ps and data from only the last 4000 ps were collected. A 10 Å cut off for coulumbinc and long range forces was adopted in each simulation.

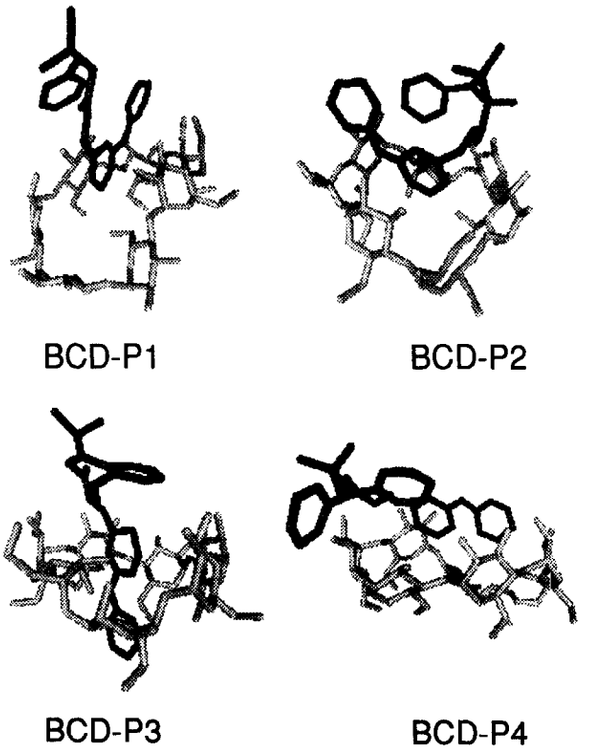


Fig. 1. Snapshots of the equilibrium configuration for each of the BCD-Pn complexes.

3. Results and discussion

The interaction energies for the examined host–guest couples are shown in Table 1. These values were calculated subtracting from the ACE of the complexes the ACE of the components alone. The main contribution to the interaction between the host and the guest molecules is due to the van der Waals interactions. The sketches of the equilibrium configuration of the complexes are shown in Fig. 1, while the computed radial distribution functions among the BCD hydroxyls (OH) and the Pn aromatic carbon atoms (CA) are shown in Fig. 2. For each of the BCD-Pn couples the $g(r)$ function exhibits a broad peak at $r \approx 5$ Å which shows the formation of the adducts. The plots in Fig. 1 show that the guest molecule approaches the larger BCD ring entering into its hydrophobic cavity with the ϕ-O-ϕ tail (where ϕ indicates a phenyl group); this finding is supported by reports of β-cyclodextrin selectivity towards molecules with two aromatic rings [15]. The P1, P2,

Table 1
Calculated energy (kcal/mol) of the BCD-Pn complexes

Complex	Energy
BCD-P1	−14.1
BCD-P2	−16.5
BCD-P3	−31.9
BCD-P4	−21.1

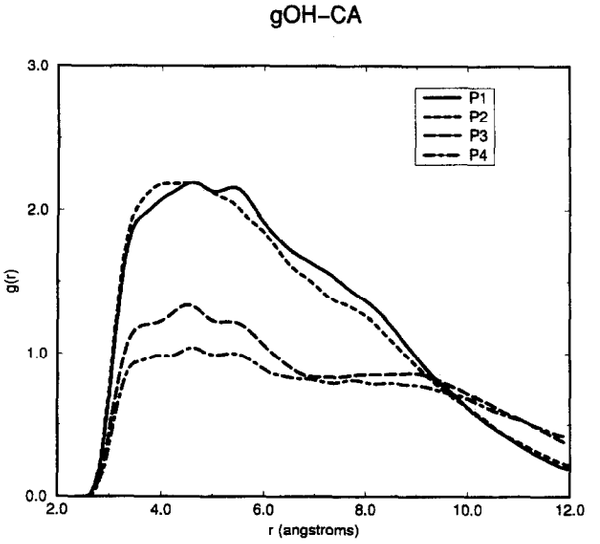


Fig. 2. Radial distribution functions among the BCD hydroxyl oxygen atoms (OH) and the Pn aromatic carbon atoms (CA).

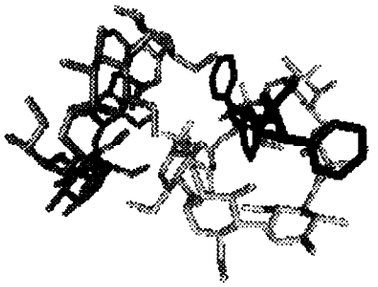


Fig. 3. Equilibrium configuration of the BCD_2-P1 complex after 5 ns MD run.

and P4 molecules do not completely enter the host cavity while the P3 molecule penetrates deeply into the BCD cavity with its longitudinal axis almost perpendicular to the BCD ring. This is probably due to the formation of hydrogen bonds between the oxygen atom in the methoxyl group (R3) and the primary hydroxyls along the BCD top torus.

Fig. 4. Sections along the $x-z$ and $y-z$ planes of the BCD-P1–water adduct after 5 ns MD run.

Twelve MD runs were performed on the systems composed by 1 pyrethroid and 2 BCD molecules starting from an initial conformations obtained by manually docking a second BCD molecule to the complexes shown in Scheme 2. In all cases, after the MD run only 1:1 complex stoichiometry was retained and the second BCD units was pulled away from the 1:1 adduct. (Fig. 3)

4. Solvent effect

The equilibrium conformation of the BCD-P1–water system is very similar to that computed in the absence of water molecules. Fig. 4 show the sections along the $x-z$ and the $y-z$ planes of the BCD-P1–water equilibrium configuration. The water molecules form a cage around the BCD-P1 complex and no water molecule penetrates inside the BCD hydrophobic cavity.

5. Temperature effect

We investigated the effect of temperature on the adduct for the BCD-P1 couple. The calculations were performed starting from the equilibrium conformation of the system at $T = 298$ K. We carried out six MD runs, each of the duration of 500 ps, in the NVT ensemble varying the Temperature from 300 to 350 K at regular intervals. We observed that, in the 350 K run the adduct geometry was broken after 250 Ps with the separation of the host–guest couple.

Acknowledgements

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