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A molecular modelling study of the interaction between β -cyclodextrin and the organophosphorothioate pesticide parathion

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The interaction between parathion and β -cyclodextrin was investigated by Molecular Dynamics. Several *in vacuo* trajectories were calculated for the system imposing a 1:1 stoichiometry. The influence of the solvent and temperature was considered. The results account for the formation of adducts which are stable at room temperature and involve mainly the nitrophenoxy group of the guest molecules which interacts with the hydrophobic cavity of the host by van der Waals forces.

Keywords: cyclodextrin, parathion, organophosphorothioate pesticides, molecular dynamics, inclusion complexes

Introduction

Cyclodextrins are a group of cyclic oligosaccharides produced by numerous micro-organisms with a ring structure which is basket-like in shape. These compounds are able to include several kinds of molecules into their internal cavity [1, 2]. The inclusion leads to important modifications of the properties of the guest compound, allowing the fixation of volatile materials, protection against oxidation and photolysis, modification of reactivity and of biological properties [3–5]. When applied to pesticides bearing esteric functions, the inclusion can stabilize the organic esters against hydrolysis. β -Cyclodextrin has thus attracted much attention for its ability to stabilize labile pesticides and to improve their residual activities [6]. In recent years molecular modelling techniques [eg molecular dynamics (MD) and molecular mechanics] have been successfully applied to the study of the interactions between the β -cyclodextrin molecule and small ligand molecules [7–12]

In this study we present the results of a series of MD experiments carried out on the inclusion complexes of the β -cyclodextrin and an organophosphorothioate pesticide, *O,O*-diethyl *O*-4-nitrophenyl phosphorothioate (parathion). The geometry of the complexes and the energies were pre-

dicted. Moreover, we took into account the effect of the solvent on adduct formation. The results agree well with circular dichroism data [13].

Materials and methods

The parathion molecule is shown in Figure 1. It is also known as thiophos or parathion-ethyl.

The β -cyclodextrin (BCD) host 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 smallest and the largest circumferences, respectively. No hydroxyl group is within the toroid cavity which, accordingly, has a pronounced hydrophobic character. As a consequence, the ability of the BCD to form inclusion complexes in aqueous solution derives from this cavity, the interior of which is less polar than water.

The MD experiments were performed by using the DLPOLY2 [14] program. The AMBER plus GLYCAM [15] force field was used with the necessary adaptations, while the partial atomic charges were calculated by a semi-empirical SCF-MO calculation using the AM1 hamiltonian [16] and the program MOPAC [17]. Calculations were carried out on an IBM RS600. The docking of the guest into the host was made according to the topologies showed in Figure 2. The conformational search via MD was performed *in vacuo* according to a simulated annealing [18]

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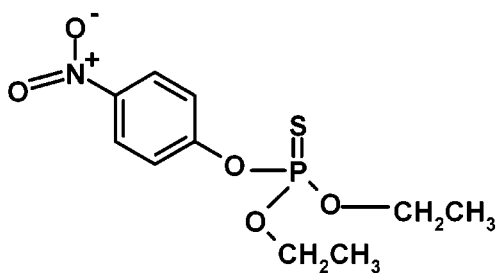
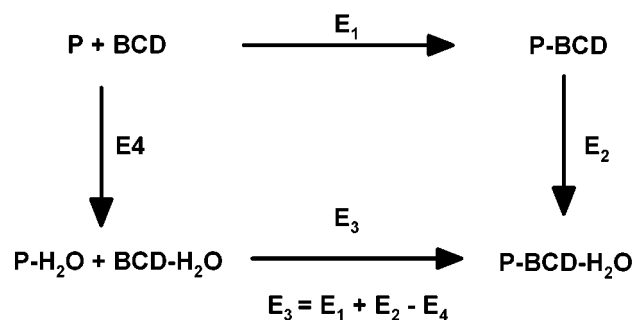


Figure 1. The parathion molecule.

scheme similar to those used by Fronza *et al.* [12] in the study of complexes between β -cyclodextrin and the indomethacin molecule. The simulated annealing was carried out between 300 and 0 K with 100 K steps, 20 ps for each temperature step followed by a set of 10 constant temperature dynamics with periodic temperature jumps between 100 and 0 K, 20 ps for each run. Each MD run was performed in the NVT (number of molecules, volume and temperature constants) ensemble using periodic boundary conditions and a 30 Å side cubic cell. The coulomb interactions were handled by a truncated shifted potential. The minimum configuration energy values are given in Table 1.

An MD simulation on the BCD–parathion system with 150 water molecules was performed in the NVT ensemble with a 25 Å-side cubic cell at a temperature of 298 K. The system was allowed to equilibrate for 100 ps and then the trajectory was collected over 300 ps. The configuration *a* of the Scheme 1 was chosen as the starting point. The above



Scheme 1. Thermodynamic cycle used to compute the interaction energy between BCD and parathion in water.

parameters were employed to perform the MD runs on the BCD–H₂O, Parathion–H₂O and the H₂O systems. The total energy values, averaged over the 300 ps run, were collected for each of the above systems and the interaction energy between the parathion and the BCD (*E*₃) was computed according to the equation given in Scheme 1.

Results and discussion

The BCD–parathion system *in vacuo*

The interaction energies computed *in vacuo* for the host–guest couples (a–f) are shown in Table 1. The values were calculated by subtracting the energies of the components alone from the energy of the complexes. The main contribution to the interaction between the host and the guest is due to van der Waals interactions. The conformer

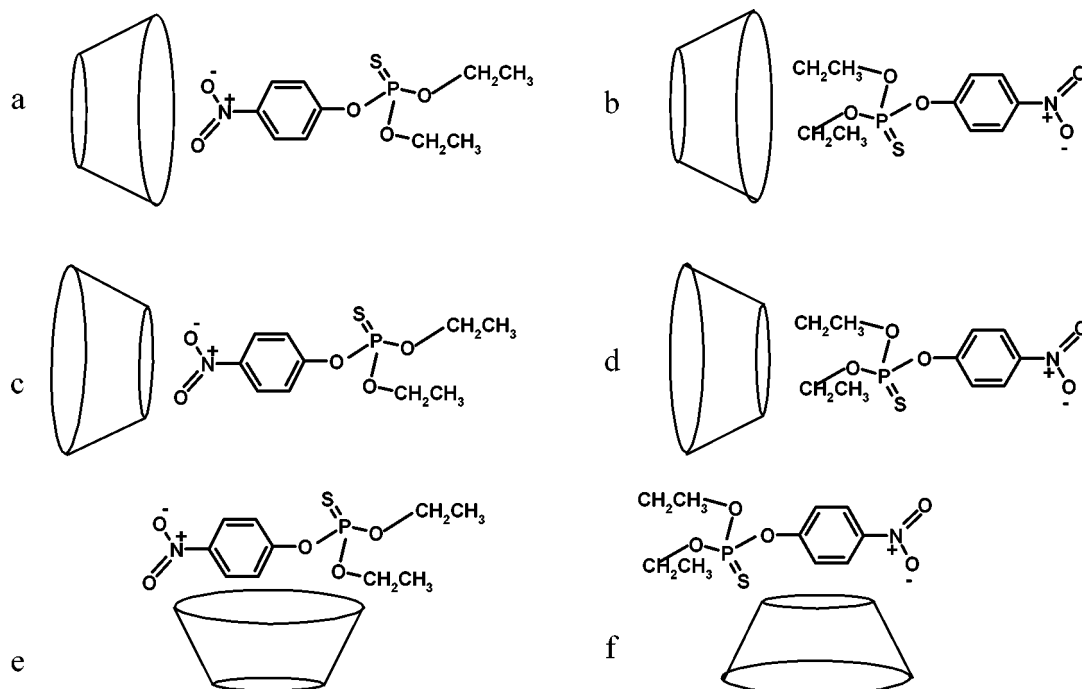


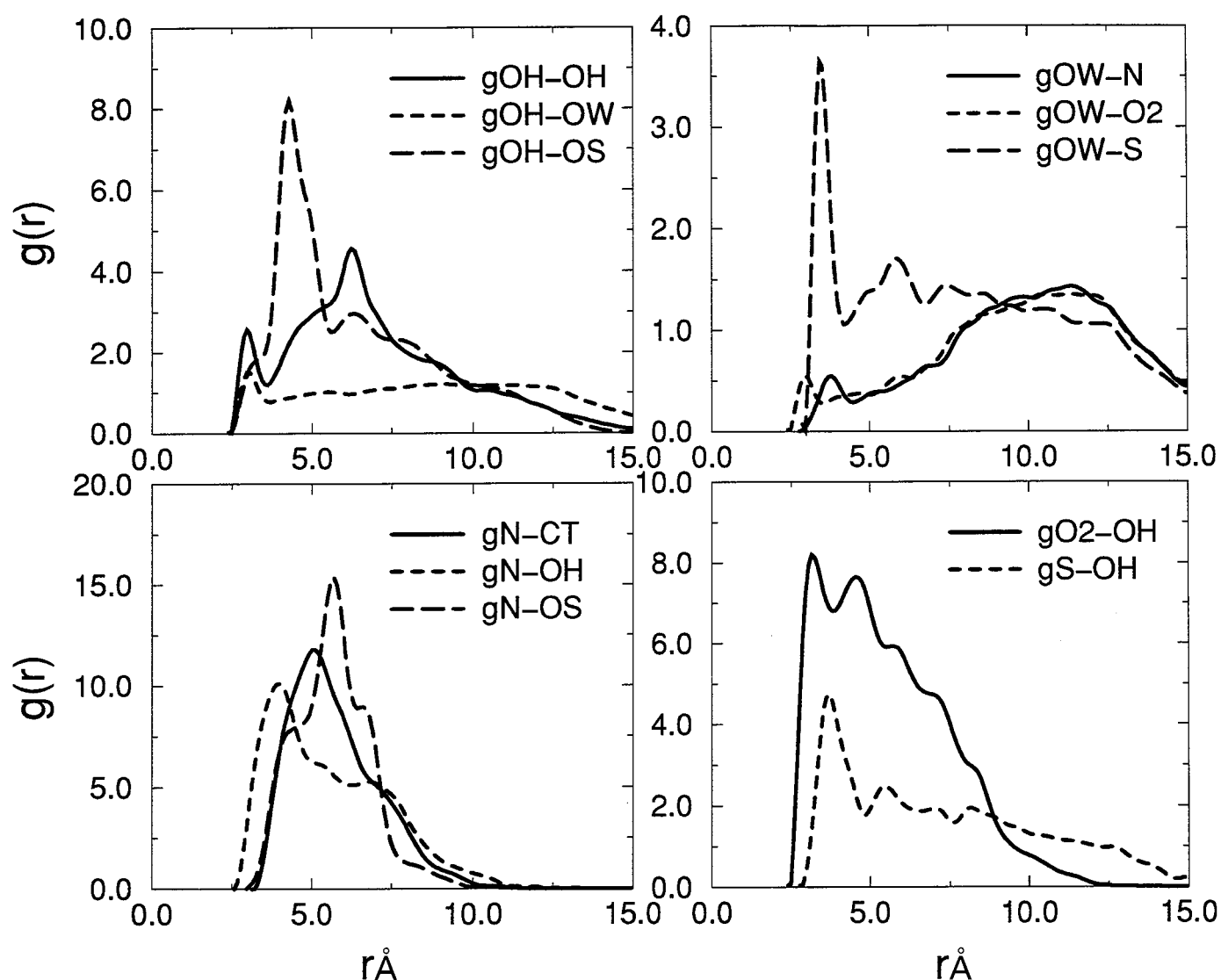
Figure 2. The different topologies taken into account for the entry of the guest molecule into the cavity of the BCD host

Table 1. Calculated energy (Kcal mol⁻¹) of the complexes between BCD and parathion

Conformer	E_{tot}^a	E_{vdW}^a	$E_{coulomb}^a$	$E_{interaction}^b$
a	+ 4.58E + 01	+ 2.18E + 01	- 1.02E + 02	- 4.91E + 01
b	- 4.08E + 01	- 2.69E + 01	- 8.91E + 01	- 4.41E + 01
c	- 3.62E + 01	- 2.79E + 01	- 7.95E + 01	- 3.95E + 01
d	- 3.34E + 01	- 2.45E + 01	- 7.98E + 01	- 3.67E + 01
e	- 2.89E + 01	- 2.31E + 01	- 8.03E + 01	- 3.23E + 01
f	- 3.25E + 01	- 2.16E + 01	- 8.01E + 01	- 3.58E + 01
BCD	+ 6.15E + 01	- 1.40E + 01	+ 1.23E + 01	
Par	- 6.48E + 01	+ 2.84E + 00	- 7.43E + 01	

^a $E_{tot} = E_{vdW} + E_{coulomb} + E_{internal}$; where E_{vdW} , $E_{coulomb}$ and $E_{internal}$ are the van der Waals, the coulomb and the internal (stretching + bending + torsion) contributions, respectively.

^b Computed as: $E_{tot} - E_{totBCD} - E_{totparathion}$, where the subscript i is over the a – f conformers.

**Figure 3.** Radial distribution functions between the parathion the BCD, and water. OW, water oxygen; OH, BCD hydroxyl oxygen; OS, BCD glycoside oxygen; O₂, parathion oxygen atoms bound to the nitrogen atom; N, parathion nitrogen; S, parathion sulphur; CT, BCD sp³ carbon atoms.

(a) is the most stable. This agrees with experimental data reported for the BCD–parathion and BCD–nitrophenol complexes [13]. The angle of the longitudinal axis of the included 4-nitrophenoxy ring relative to the symmetry axis of the top cavity from the bottom to the top torus (Θ_{ins}) was computed and, owing to the distorted structure of the BCD, the angle was approximated to $10 \pm 5^\circ$. Induced circular dichroism spectra of the BCD–parathion complexes [13] allowed computation of a value of 6° for Θ_{ins} which is not very close to our determination, suggesting that the parameters employed in the force field should be improved.

The BCD–parathion–H₂O system

The E_3 value, computed according to the equation given in Scheme 1, was $-84 \text{ Kcal mol}^{-1}$. The radial distribution functions between the parathion, BCD, and the water atoms are shown in Figure 3.

The gOH–OH, gOH–OS radial distribution functions show a pattern of intramolecular hydrogen bonding in the BCD molecule which appear to be more consistent than the hydrogen bonding between the BCD molecule and the water molecules. Also the O₂ atoms in the parathion molecule form hydrogen bonds with the BCD hydroxyls as shown by the gO₂–OH function. The pronounced peaks and shoulders in this function suggest that the O₂ type oxygen atoms hardly move from their equilibrium position. The radial distribution functions between the OW and the N, O₂, and S atoms in the parathion molecule show that the S atom in the parathion tail exhibits about three solvation shells; while both the O₂ and N atoms which enter the BCD cavity exhibit only one water shell at 3 and 4 Å, respectively. This suggests that the preferred orientation of the parathion molecules which enter the BCD cavity is the NO₂ head. The gN–CT function exhibits a marked peak at $r = 5 \text{ Å}$ and smoothly decreases through a shoulder at $r = 7 \text{ Å}$; the gN–OH function shows a peak at $r = 4 \text{ Å}$, with smaller shoulders at 5 and 7 Å, and the gN–OS function has a sharp peak at $r = 6 \text{ Å}$ with shoulders at $r = 4$ and 7 Å, respectively. These values are consistent with the proposed motion of the parathion molecule inside the BCD cavity. The radius, indeed, is about 5–6 Å in the middle of the cavity. In particular, the peak at $r = 5 \text{ Å}$ in the gN–CT functions indicates the presence of the nitrophenoxy ring inside the hydrophobic BCD cavity. Finally, the peak at $r = 4 \text{ Å}$ in the gS–OH function evidences the inclination of the longitudinal axis of the parathion molecule.

The results are consistent with a good qualitative description of the BCD–parathion adduct formation. The force field parameters, however, could be improved to obtain a better reproduction of the insertion angle of the host molecule. We are currently working on this aspect in order to perform MD studies on the interaction of different organophosphorothioate molecules with normal and substituted BCD rings.

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