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Electronic structure and driving forces in β-cyclodextrin: Diclofenac inclusion complexes

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Abstract

We investigate the geometry and electronic structure for complexes of β-cyclodextrin with diclofenac using DFT calculations. The effect of solvent is explicitly taken into account. This investigation allows us to draw meaningful conclusions upon the stability of the complex and the nature of the driving forces leading to the complexation process. In particular we emphasize the role of the water, by pointing out the changes in the solvent's electronic structure for different docking geometries.

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1. Introduction

Cyclodextrins (CD) are cyclic oligosaccharides composed of six, seven or eight α-1, 4-linked glucose residues and are characterized by a truncated cone shape. In their cavity, the CD can accommodate a wide class of organic molecules leading to inclusion complexes [1]. CD chemistry has caused much interest, not only due to its applications to pharmaceutical science and technology but also because the inclusion represents an ideal model mimicking enzyme-substrate interactions [2,3]. In addition, the study of host:guest interaction may lead to a better understanding of some fundamental topics (i.e. the nature of the hydrophobic interaction).

Diclofenac (DCF), 2-(2′,6′-dichloroanilino) phenylacetic acid is a non-steroidal anti-inflammatory drug used in different diseases such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis or sport injuries. Its geometry with two twisted aromatic rings plays an important role in this property [4].

Experimental studies for both α, and β-CD complexes revealed that a 1:1 stoichiometry characterizes them [5–11]. Previous work suggests that hydrophobic effects and hydrogen bonding plays an important role in the complexation process [7,9]. By comparing results on α-CD:DCF [5] and β-CD:DCF [6] Arancibia et al. suggested that physical interactions in both complexes have a similar nature. Also they suggested that in the case of β-CD:DCF the aromatic ring bonded to an acetate group resides within the β-CD cavity. NMR studies on β-CD:Na–DCF complexes [10] have recently provided the evidences for the presence of two isomeric 1:1 complexes. The values for the binding constants obtained with specific protons of both compounds reveal the correlation between the protons inside of the β-CD cavity and both the aromatic rings of the DCF–Na, supporting the hypothesis of bimodal binding process.

In a more general picture, the driving forces involved in the complexation have been attributed to factors including van der Waals force [12], dipole–dipole interactions [13] hydrophobic effect [14] or charge transfer [15]. Van der Waals are the long range forces arising between two molecular clusters; the dipolar interaction arises when the two molecules have a dipole moment. The hydrophobic interaction (HI) arises between two non-polar molecules; they are widely believed to play a

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dominant role in the formation of large biological molecules. Nevertheless the mechanism of HI is still under debate [16–18]. In the "classical" theory, the distribution of water molecules around the solute is a key feature of the phenomenon. The enthalpy and entropy changes of the process are both positive; the association is said to be "entropy driven". More recent theories suggest that the hydrophobic interaction arises from electrostatic fluctuations, changes in water structure or the interplay of density fluctuations at both small and large length scales [18]. Finally, the mechanism of the charge transfer interaction can be summarized as following: when a molecular complex is built up from two components a mixing of the filled orbitals of the first molecule with the vacant orbitals of the second appears. A charge transfer between the two monomers arises, leading to an attractive force between the two components.

By means of ab initio calculation we perform a detailed analysis of the geometric and electronic structure of the β-CD:DCF complex. Our main tool is the analysis of the projected density of states (PDOS) onto the atomic orbitals of the two components of the system. We extract physically meaningful information by comparing the PDOS of the free systems with that of the complex. In addition we report the binding energies and the dipolar moments, computed at different geometric structures of the host:guest complex.

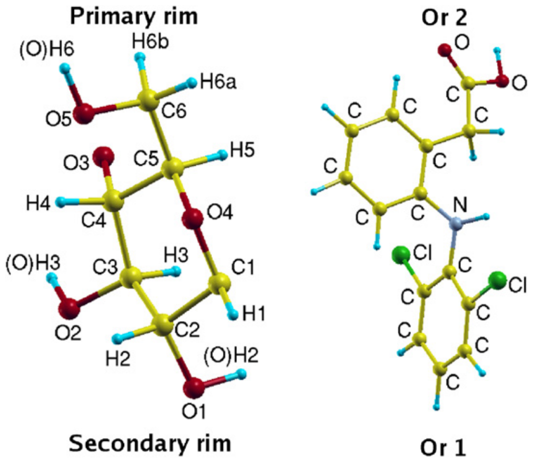

Fig. 1. Geometric structure and numbering scheme (according to our input file) for the glucopyranosic unit (left) and DCF (right); "Or. 1" and "Or. 2" indicate the position of the CD relative to the DCF in the complex (right).

2. Computational details

The structure of β-CD was built up using the data from Cambridge Structural Database [19]. The structure of DCF was built up using the molecular builder included in Hyperchem. This guess structure was optimized at ab initio level. The resulting structures are given in Fig. 1.

We take into account two relative orientations of the β-CD:DCF complex: (a) the diclorphenyl ring of DCF was oriented to the center of mass of the β-CD (we call this the 'orientation 1') and (b) the phenylacetate moiety of DCF was oriented to the center of mass of the β-CD (the 'orientation 2'). Our results are based on a periodic DFT study. To this end we use the SIESTA package [20,21]. The whole system is confined into a cubic periodic cell (the cell parameter is $a = 19$ Å). 24 water molecules are included into each cell. We use a DZP basis set with an energy shift of 100 meV. For all atoms we use Troullier–Martins pseudo-potentials [22]; as exchange–correlation functional we use GGA [23].

In order to relax the geometry of the system we perform a simulated annealing calculation; we set the initial temperature at 300 K and the target temperature at 5 K. The time step for the dynamics was 1 fs. We need 700 time steps (for orientation 1) and 600 time steps (for orientation 2) in order to reach the target temperature. The final gradients in the system were less then 5×10^{-3} Ha/Bohr. The resulting structures are presented in Fig. 2.

In the last step we compute the PDOS of the host:guest systems. Finally, we remove the water molecules and recalculate the PDOS at the same host:guest geometry.

3. Results

The PDOS for different types of atoms in the glucopyranosic unit of the free β-CD is given in Figs. 3 and 4. In Fig. 3 we

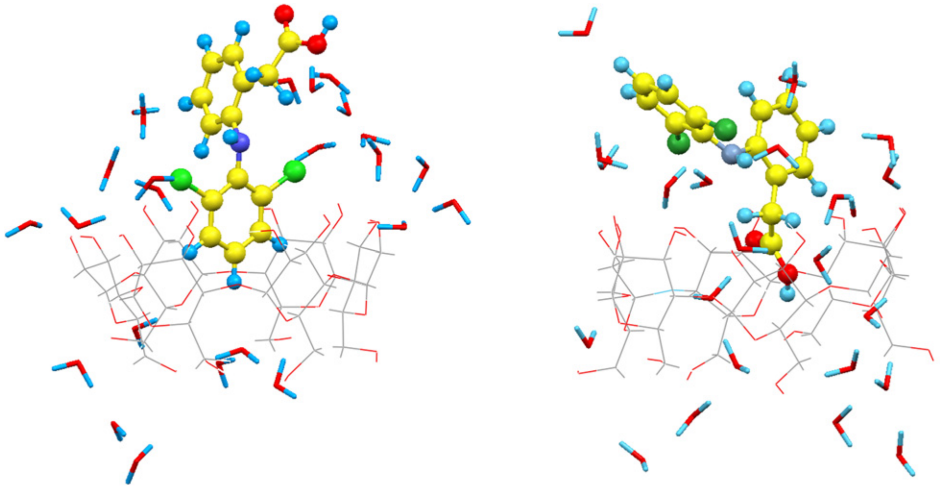

Fig. 2. Geometric structure of the complexes after the relaxation. Left: orientation 1; right: orientation 2.