CALCULATION OF INCLUSION COMPLEX OF A BINAPHTYL DERIVATIVE AND β-CYCLODEXTRIN USING DENSITY FUNCTIONAL THEORY

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Abstract

We investigated the interaction of the host-guest β-cyclodextrin-2,2'-Dihydroxy-1,1'-binaphthyl complex by means of molecular dynamics simulation using a density functional based tight-binding code. We focused in particular on the investigation of the most stable conformation of this complex by investigating some of the structural properties that change with the time. This includes the hydrogen bonding formation of the active agent guest molecule with the torus-like macro ring of the host β-cyclodextrin leading to the formation of the stable adduct in the lipophilic cavity of the biopolimeric matrix. The role of solvent, water in stabilizing the complex was also discussed. We relate our results of the final stable optimized geometry of the complex to the UV/Vis and circular dichroism spectral study.

Keywords: β-cyclodextrin-2,2'-Dihydroxyl-1,1'-binaphthyl inclusion complex, density-functional theory

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1. INTRODUCTION

The density functional tight-binding code (DFTB) combines the efficiency of semi-empirical quantum-chemistry and tight-binding approaches with the transferability of more sophisticated density functional methods . It has been widely used to study biomolecules with atoms of different electronegativities and different bonding types, ranging from covalent, ionic bonding to hydrogen bonding and van der Waals-type interactions (Elstner, Porezag, Jungnickel, Elsner *et al.*, 1998). We have applied this method to cyclodextrins which constitute an important family of the inclusion compound. Cyclodextrins are truncated doughnut-shaped cyclic oligosaccharides molecules consisting of α-1,4 linked D-glucose units with a hydrophobic interior surface and a hydrophilic external surface. The most prominent and abundant of the cyclodextrins are α, β and γ cyclodextrins with six, seven and eight glucose units respectively. They are produced by degradation of amylose by glucosyltransferases, in which one or several turns of the amylose helix are hydrolysed off and their ends are joined together to form cyclic oligosaccharides called cyclodextrins or cycloamylases. They have the ability to form inclusion compounds, acting as hosts, by allowing other molecules (guests) into their hydrophobic cavity (Atwood, Davies, D. D. MacNicol and Lehn, 1996), (Lipkowitz, 1998) and (Saegner, Jacob, Steiner, Hoffman *et al.*, 1998). In various sizes and chemical characteristics they are being used in pharmaceutical chemistry as drug delivery systems, in chromatography and as enzyme catalysis models or assistants in protein folding (Szejtli, 1997). The topology of one of the family is as shown in Fig. 1. Of particular interest of these mentioned applications are inclusion complexes with organic binaphthyl derivatives (BNP). 2,2'-Dihydroxy-1,1'-binaphthyl is a chiral molecule, which exits in enantiomeric form as shown in Fig. 2. These molecules are sources of the most important family of auxiliaries, ligands and catalysts employed in the enantioselective reactions. The inclusion complex study of this compound is important to offer information about the stable adduct in the catalytic reaction.

In this study we present the results of structure optimization and molecular dynamics (MD) simulation for one of the enantiomeric pair (R) of 2,2'-dihydroxyl-1,1'-binaphthyl. The optimization of the complex in the crystalysed form without solvent water was first carried out in order to have the initial information about how the complexation pathway should proceed. After this, we solvated the whole complex in the water which provides the driving force for the complexation and further stabilization of the complex using the predicted complexation pathway earlier obtained from the unsolvated form. The most obvious candidate properties from simulation that might indicate the stability of these complex are a number of structural properties that describe the structure over time. One of these is the evolution of the geometry of the guest molecule inside the cavity of the BCD and the formation of the hydrogen-bonded network of the complex. The energy of various trial

configurations of the guest molecule inside the cavity of the host as well as geometrical evolution of the guest molecules are reported. The role of water as the solvent in the stabilization of the complex are also reported. The results are discussed with respect to the UV/Vis and CD spectra.

2. COMPUTATIONAL DETAIL

All the initial geometries used in this calculation were first relaxed using the conjugate gradient relaxation method of the DFTB. The DFTB shows that both the R and S BNP preferred a twisted geometry of the aromatic planes to perpendicular planes as shown in Fig.2. The geometry has the energy lowered by about 0.034 eV compared with the perpendicular geometry. The calculation confirmed by using another density functional theory code (VASP) suited for ab-initio molecular dynamics simulation also shows a lower energy difference in favour of twisted geometry with dihedral angle ϕ(C5-C8-C17-C21) equal to 67.3^o and -67.3^o for R and S BNP respectively (Kresse and Futhmüller, 1996) while the DFTB method shows a respective dihedral angle 63.4^o and -63.4^o. The geometry optimization of the R-BNP inside the β-cyclodetrin is then followed. We considered the different topologies of entry of the guest molecules (R-BNP) inside the host (BCD) in order to search for the possible minima of the complex. The starting geometry for β-cyclodextrin, 'SIBJAO', was taken from the Crystallographic Database (Ding, Steiner and Saenger, 1991). The trial orientation of the R-BNP inside BCD was done according to the Fig. 3 below. R-BNP was inserted from both the primary wider end (shown) and the secondary narrower ends (not shown) in a longitudinal (axial) and transverse (equatorial) direction according to the illustration diagram A and B of Fig. 3. We focus our attention at the moment on the calculation of the inclusion complex of the R-BNP using the DFTB method.

The conjugate gradient relaxation of (A) and (B) were carried out and the energy of both were compared. This is then followed by the MD simulation in vacuo without periodic boundary condition at room temperature starting from the optimized geometry using an MD time step of 0.5 fs in order to monitor how the structure evolves in the complex. This provides the useful information for which of these trial conformations is the preferred orientation before the final solvation of the complex is done in order to save computational time. The results of these simulations are shown in Figures 5 and 6. The geometry fluctuations of these structures during the MD run were measured.
The preferred geometries for R-BNP complexed with BCD were then solvated with addition of 119 molecules of water in the bounding cubic box of dimension 25x25x25 Å^3. The relaxed geometry of the host-guest-water is shown in Fig. 7.

3. RESULTS AND DISCUSSION

After the relaxation, the planes of biphenyl, (R- and S-BNP) shown in Fig. 2 are inclined with dihedral angles ϕ(C5-C8-C17-C21) equal to -63.4^o (use Fig. 4 for reference of the labelling) with the same binding energy. This binding energy is lower by about 0.034 eV in favour of the twisted geometry according to the DFTB method as reported in Section 2.
The conformation shown in Fig. 3 with docking of the BNP along the axial of the wider cavity is found to be stable according to Figures 5, 6 and 7 which show the results of the complex of R-BNP with BCD in vacuo. The snapshots from movies in Fig. 5 shows the encapsulation of the BNP in the hydrophobic cavity of BCD. There was deformation of the BCD structures after 1000 fs before returning to its doughnut shape with BNP always entrapped in the centre of the cavity. Fig. 7 shows the instability in the geometry as the BNP evolves from its relaxed complexation with BCD. BNP was totally out the cavity of BCD which means that the complexation is not favoured in this equatorial direction. The diameter flexibility of the BCD is not enough to entrap the BNP in this direction.

Figure 8 shows the relaxed structure of the host-guest (R-BNP) complex in 119 water molecules in a simulation with a cubic box of dimension 25x25x25 Å^3. Molecular dynamics simulation of the structure in Figure 8 was subsequently performed for 2250 fs. The structural properties obtained from this simulation is shown Fig. 9. Figure 9 (A) shows the radial distribution functions between the water oxygen atoms (OW) and the BCD molecule hydroxyl (OH) and glycosidic(OS) oxygen atoms. The g_{OW-OW} function is almost equal to that computed for bulk water. The radial distribution function between the BCD hydroxyl oxygen atoms (OH) and the water atoms (OW) reveals the existence of two shells of water molecules around BCD at r = 3.0 (small sharp peak) and r = 5.3 Å^3 (broad peak) respectively as shown in the Figure 9 (A) in agreement with the calculation done by Manuza et. al. (Manunza, Deiana, Pintore and Gessa, 1997) using the DLPOLY(2) program. Figure 9 (B) shows the radial distribution functions between BCD hydroxyl (OH) and glycosidic (OS) oxygen atoms. In the equilibrium conformation the hydroxyl groups of the BCD molecule link together with the glycosidic oxygens via the formation of hydrogen bonds, as evidenced by the peaks of $g_{OH-OS(BCD)}$ in Fig. 9 (B). Figure 9 (C) shows the radial distribution functions between the water oxygen atoms (OW) the BCD carbons C atoms. The first shell of water molecules is around 3.6 Å leading to the first broad peak of $g_{OW-C(BCD)}$. The position of the peak agrees with the report of about 3.6 Å for methane-water system (Lipkowitz and Anderson, 1994). Also shown is the radial distribution function between the water oxygen (OW) and (OH) of BNP. The two pictures confirm the hydrophobicity of the inner cavity of BCD. No water molecules was found inside the BCD cavity due to the hydrophobicity of the cavity and the presence of the guest

BNP molecule occupying the central region.

Figure 9 (D) confirms the formation adduct of the host (BCD)-BNP complex with the formation of hydrogen bonding between the hydroxyl group of the BNP and the glycosidic oxygen atoms of BCD as indicated by the first peak in $g_{OH(BNP)-OS(BCD)}(r)$. The position of the peak is around 2.85 Å. This indicates the presence of biphenyl aromatic rings of binaphtyl inside the hydrophobic cavity of BCD. Water molecules form a network of hydrogen bonds with both the primary and secondary hydroxyl groups.

4. CONCLUSION

Our analysis of the molecular dynamics simulation based on the results of tight-binding density functional has been able to highlight the interaction between the BCD (host) and the BNP (R enatiomers) guest. The structure of the complexation correlates with the data obtained from from UV/Vis and circular dichroism spectral study in which a family of BNP was encapsulated in the the biopolymeric matrix of BCD (Bortolus, Marconi, Monti, Grabner *et al.*, 2000). The chiral separation ability of BCD on both R and S enantiomers of binaphtyl is of interest. Many experimental and theoretical studies have been carried out on varieties of guest compounds which are chiral (Kano, Kato and Kodera, 1996). The density functional theory study of enantioselectivity of BCD on binaphyl is still on the way.

Acknowledgements

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FIGURE CAPTIONS

Figure 1: Topology of β-cyclodextrin

Figure 2: Enantiomeric pair of binaphtyl (R and S).

Figure 3: Sketch of the different topologies for the entry of the guest (R-BNP) molecule inside the host BCD through the wider end of the cavity.

Figure 4: (R)-BNP for reference labelling.

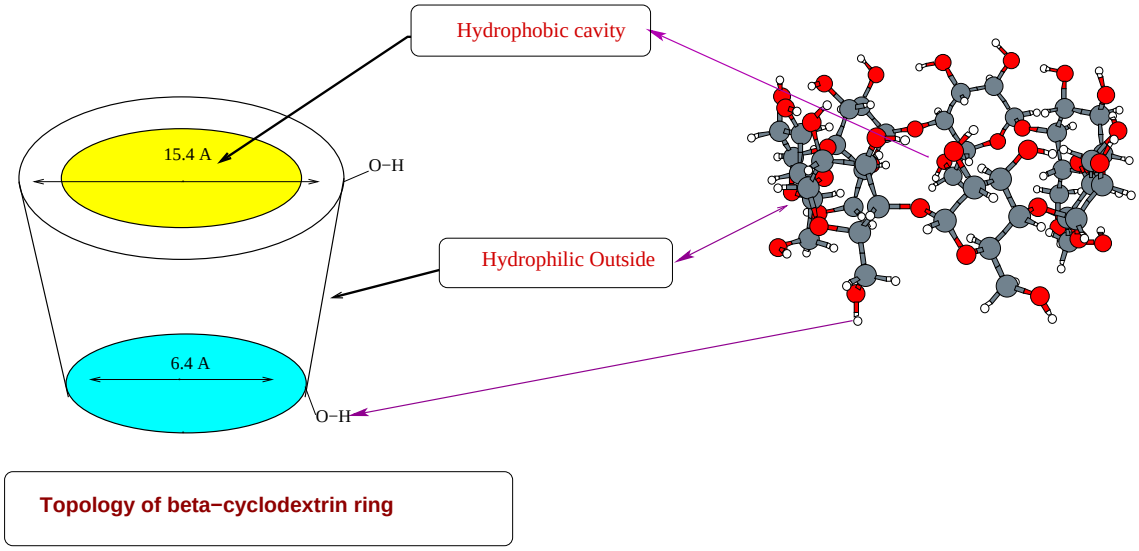
Figure 5: Time evolution of β-cyclodextrin-2,2'-Dihydroxyl-1,1'-binaphthyl complex during the MD run at 300 K (from topology A).

Figure 6: Time evolution of β-cyclodextrin-2,2'-Dihydroxyl-1,1'-binaphthyl complex during the MD run at 300 K (from topology B).

Figure 7: Evolution of the dihedral angle ϕ(C21-C17-C8-C5) for the trial conformations in A and B. A1 is the trial from the wider end of the cavity in the axial direction and A2 from the narrower direction. B1 is the equatorial trial from the wider open and B1 from the narrower in same axial direction. A1 and A2 shows some stability with regular fluctuations of the ϕ(C21-C17-C8-C5) while B1 and B2 shows some irregular fluctuations. This can be compared with snapshots shown in Figures 5 and 6.

Figure 8:The relaxed geometry of β-cyclodextrin-binaphtyl in water.

Figure 9: (A)Radial distribution functions (RDF) between the water oxygen atoms (OW) and the BCD molecule hydroxyl (OH) and glycosidic (OS) oxygen atoms. (B) RDF between BCD hydroxyl (OH) and glycosidic (OS) oxygen atoms. (C) RDF between the water oxygen atom (OW) and the BCD carbons C atoms. Also shown is the RDF between the water oxygen (OW) and the (OH) of BNP. (D) RDF of the hydroxyl group (OH) of BNP and glycosidic (OS) oxygen atoms of BCD. The first peak shows the formation of hydrogen bonding with OS atoms of BCD. Also shown in (C) is the RDF for carbon atoms of BNP with carbon atoms of BCD, and the RDF of the aromatic carbons of BNP and hydroxyl groups of BCD. All these pictures in (C) confirms the encapsulation of the of guest (BNP) molecule inside the cavity of BCD.



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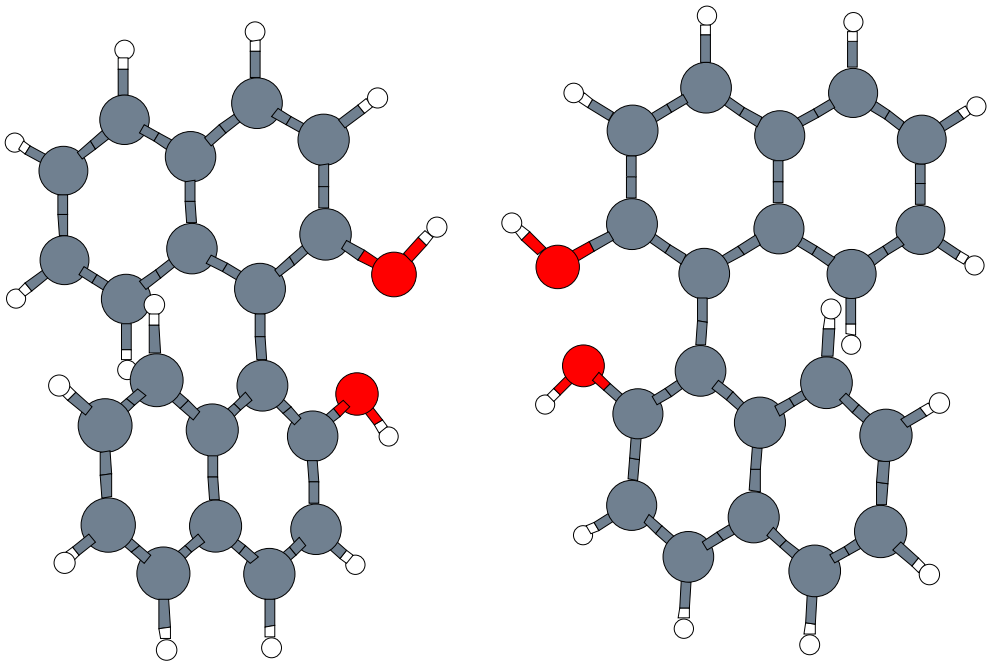

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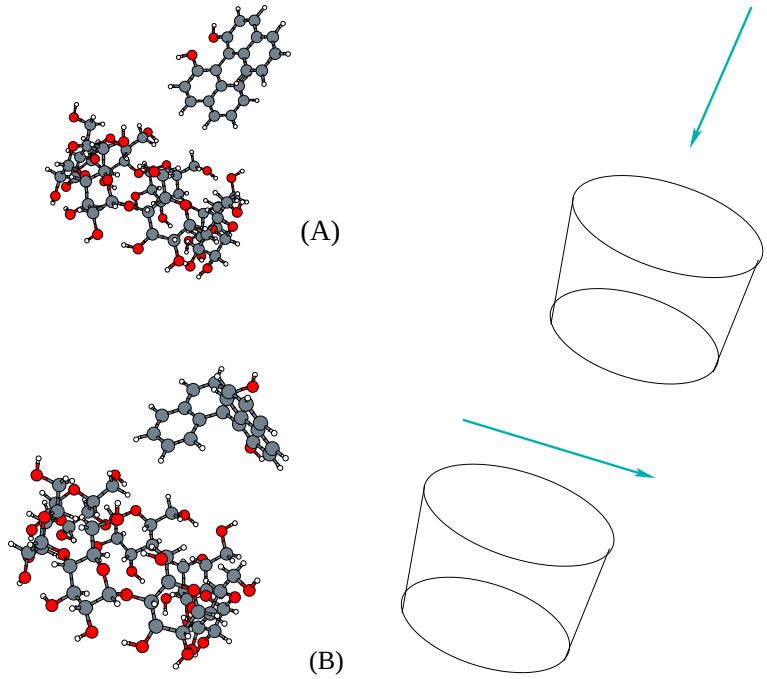

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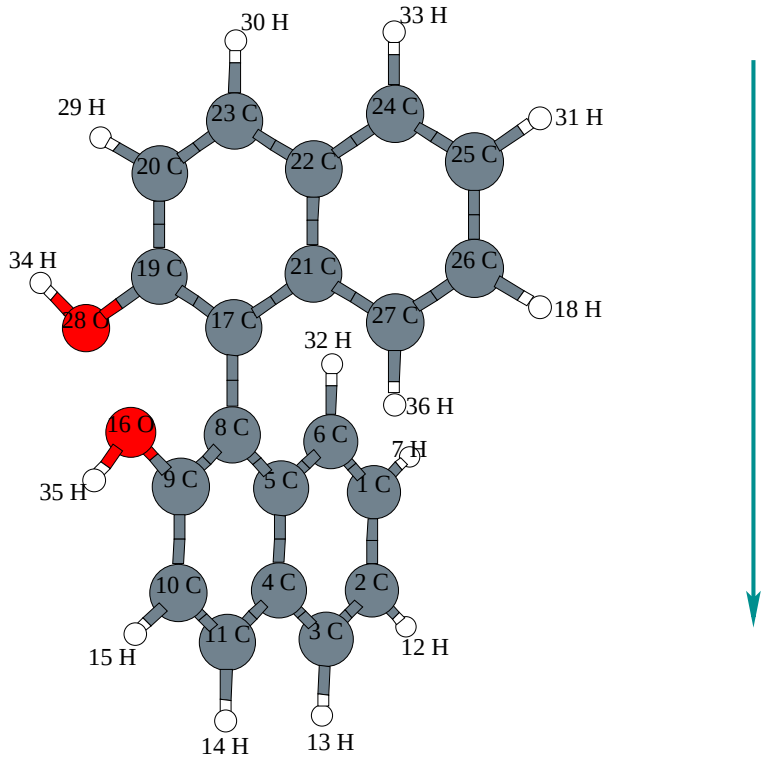

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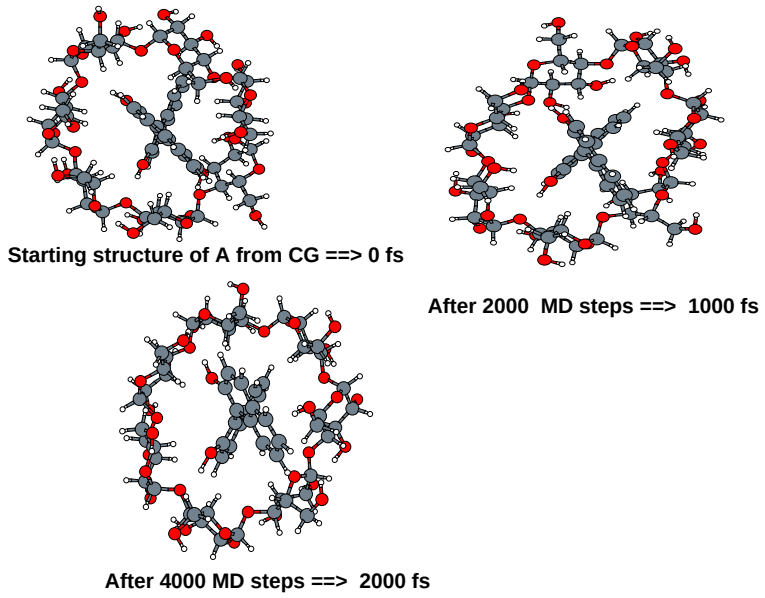

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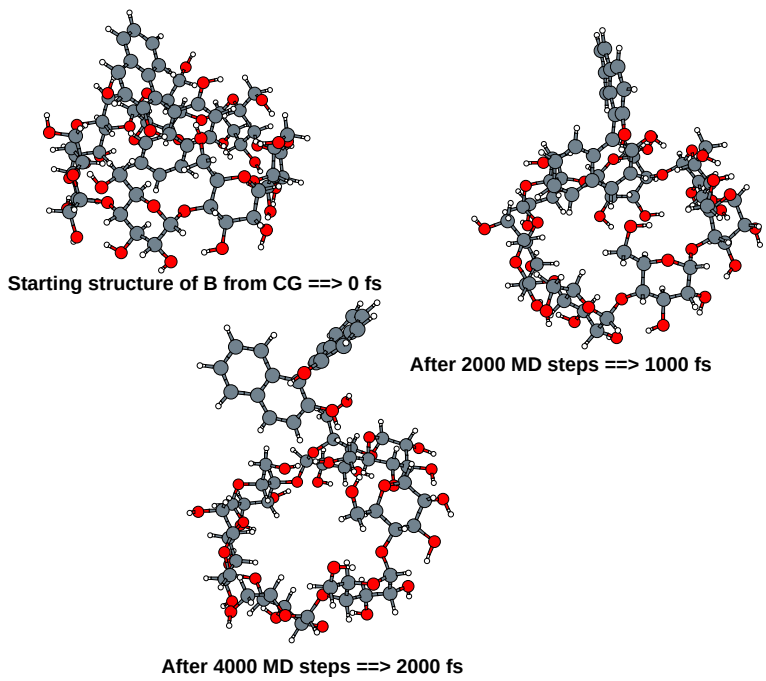

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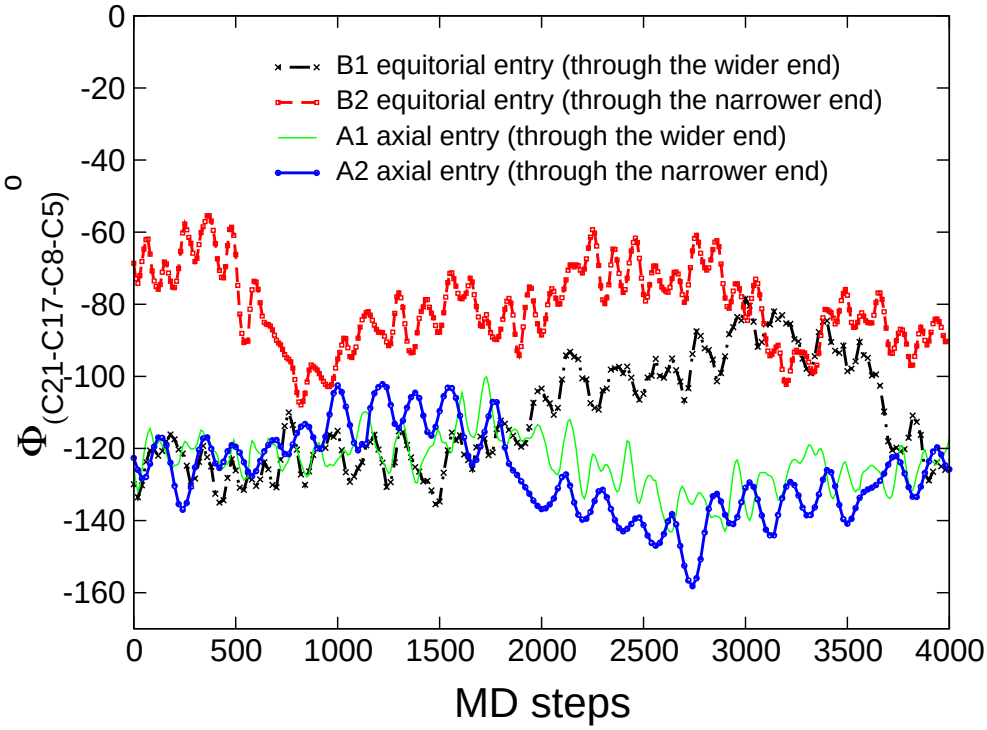

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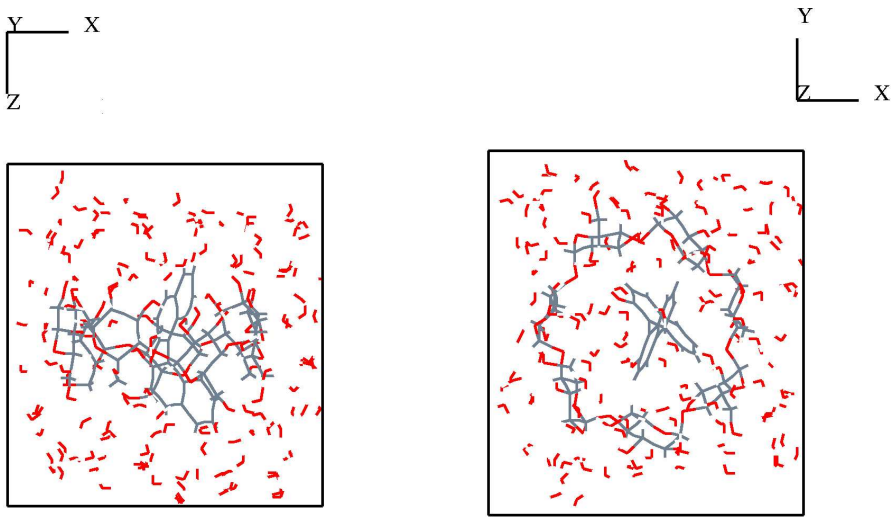

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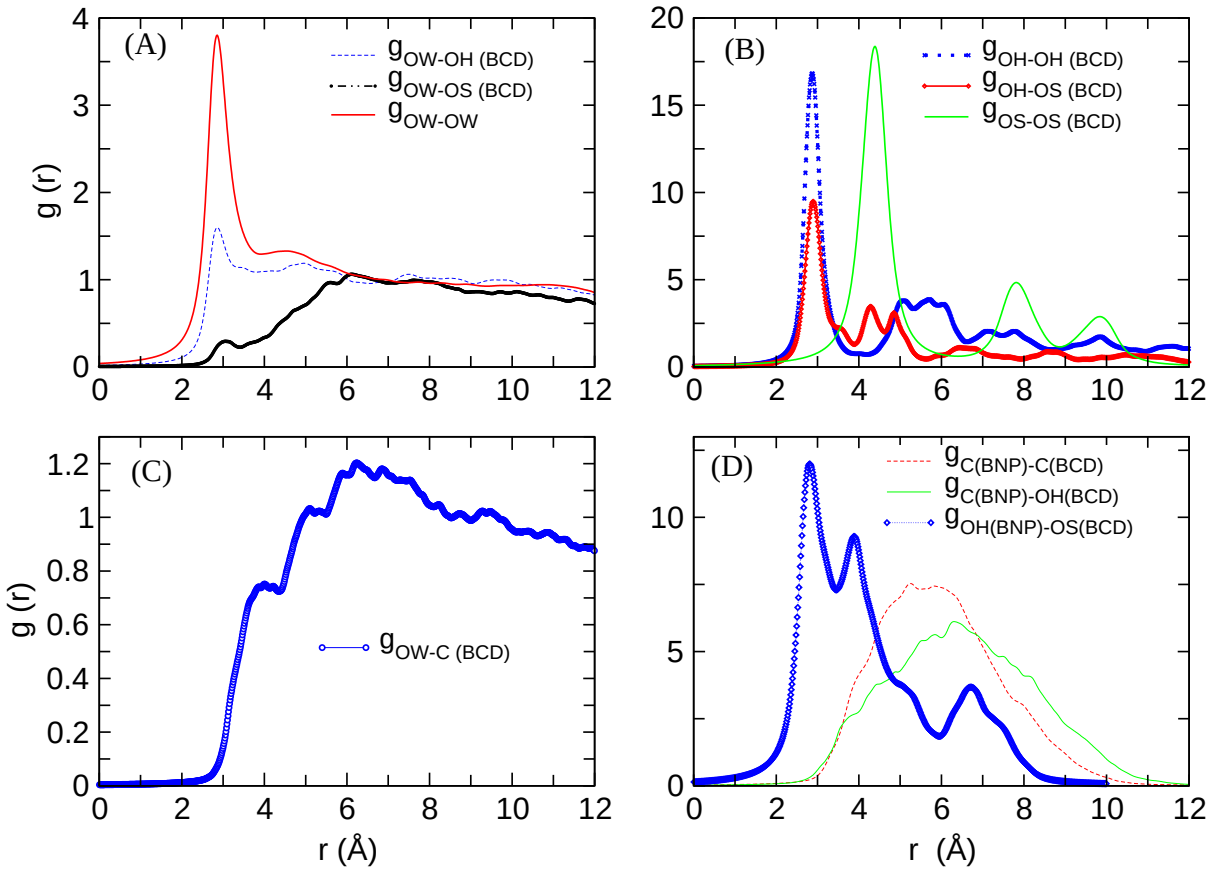

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