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Review

Molecular dynamics and quantum mechanics study of the [2-oxo-*N*-phenyl-3-oxazolidinesulfonamide@β-cyclodextrin] complex

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ABSTRACT

This article describes the processes of the formation of 2-oxo-*N*-phenyl-3-oxazolidinesulfonamide@β-cyclodextrin (ONPOS@β-CD) complex with molecular dynamics and quantum mechanics with the aim of determining the most important driving forces of the complexation.
According to the results obtained from molecular dynamics simulation, hydrophobic forces are the most significant driving forces; whereas quantum mechanics calculations give rather hydrogen bonding interactions the predominate one in the complexation process.

Contents

1. Introduction

The oxazolidinones are a class of compounds containing 2-oxazolidone group in the structure. They are a class of synthetic antimicrobial agents which have activity against multiple-resistant Gram-positive pathogens, including MRSA, penicillin-resistant streptococci and VRE [1–5].

The sulfonamides are the compounds having a sulfonyl group linked to an amide group. They have various biological activities such as anti-bacterial, hypoglycemic, diuretic, anti-carbonic anhydrase, anti-inflammatory, anti-cancer activities, anti-hypertensive, anti-convulsing and herbicidal properties for potential agricultural applications [6–12].

It has seemed so interesting to Barbey et al. of coupling the two functions. Thus, they have synthesized 2-oxo-*N*-phenyl-3-oxazolidinesulfonamide, a new compound with both functions. This new compound was predicted to have a high potential biological activity [13].

However, a low chemical volatility, as well as thermal decomposition or photochemical instability can constitute a handicap to its use. Also, the biological medium mostly made up of water can cause problems to drugs essentially due to their poor aqueous solubility. Based on these, the encapsulation in the β-CD cavity can be used as a solution to these problems [14–20].

The β-CD molecule has the ability to form inclusion complexes with a variety of organic molecules stabilized only with non-covalent interactions. In addition to its protective role, the β-CD molecule can be used as conductor vector for the drug through the different tissues for reaching

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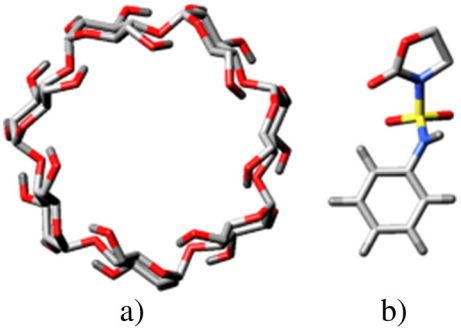

Fig. 1. Top view of (a) β-CD. (b) ONPOS.

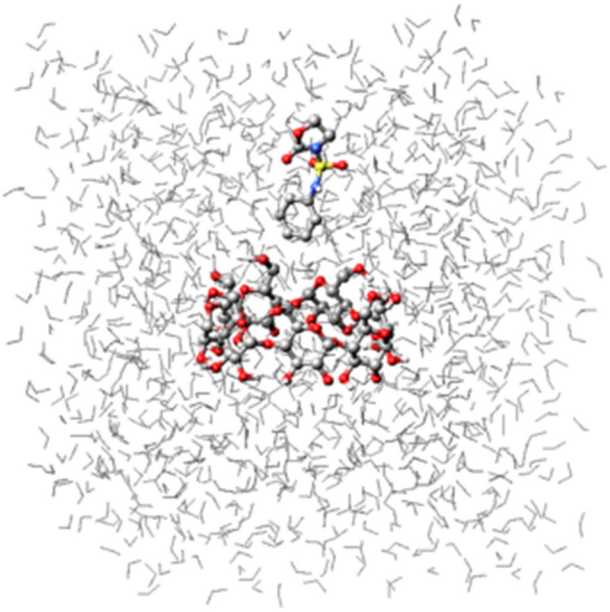

Fig. 2. The initial state of the simulation of the complexation of β-CD with ONPOS.

the biological medium. Once the complex arrived at the target, the drug must be easily released for producing its activity. Thereby, the stabilizing interactions between β-CD and the drug should not be highly important in a biological medium so that the drug release can be easily performed [21].

The determination of the non-covalent interactions herein called driving forces such as electrostatic energy, van der Waals interaction, hydrogen bonding, hydrophobic interaction, release conformational strain, exclusion of cavity-bound energy water and charge transfer, can be made essentially with computational chemistry methods [22].

Therefore, it appears to be a promising field to use molecular dynamics and quantum mechanics of following some driving forces in the complexation of ONPOS with β-CD.

In the current computational work we have studied the formation process of the ONPOS@β-CD complex using molecular dynamics and quantum mechanics for determining the most driving forces involved. Then, a comparison study was done between the results of molecular dynamics and quantum mechanics. It is important to note here that QM and MD methods have two different approaches which are complementary for predicting the driving forces in the formation of the inclusion complexes. Thus, in QM calculations all the properties, are entirely assessed with respect to the lowest energy minimum structure representing the ground state. Such calculations are too time-consuming. However, the calculations are much faster when the solvent effects are implicitly modeled. However, with MD simulation, the calculations of the are performed on many configurations generated along the complexation process using a simple force field of molecular mechanics. Also, the simplicity of the equations allows modeling the solvent effects explicitly.

2. Methods

The initial structure of β-CD was built with the help of Chemoffice 3D ultra (version 6, Cambridge software) and the geometry of ONPOS was extracted from a PUBCHEM compound database. Both structures were optimized using a B3LYP/6-31G(d) method using Gaussian 09 quantum mechanical package [23].

3. Molecular dynamics

We have used the graphical interface of Chemoffice 3D-ultra (version 6, Cambridge software) for preparing the starting system of the molecular dynamic simulation. β-CD was placed in the center of XYZ coordinate system, in a way that all the glycosidic oxygen atoms will be onto the YZ plane. Then, ONPOS was placed on the X-coordinate axes at a distance equal to 10 Å from the center. The force field parameters for both molecules were generated by the automated topology builder (ATB). See Fig. 1.

The molecular dynamic simulation was carried out using GROMACS package (version 4.0.5). The GROMOS96 force field and simple point charge (SPC) water model were used in a cubic box under periodic boundary conditions. The simulation was performed in the isobaric-isothermal ensemble (NPT) with a constant pressure of 1 bar and a temperature of 298 K controlled by Berendsen thermostat. The long-range electronic interactions were treated by the particle mesh Waals (PME) method with a 1.2 nm cutoff distance and the short-range van der Waals interactions were modeled using a cutoff of 1.4 nm.

The system consisting of both ONPOS and β-CD molecules was placed in the center of the box of 17 × 15 × 14 Å, containing 800 water molecules (Fig. 2). Then, the whole system was relaxed using the steepest descent algorithm.

The system was firstly heated by small increments from 0 to 289 K during 300 ps, followed by an equilibration step performed during

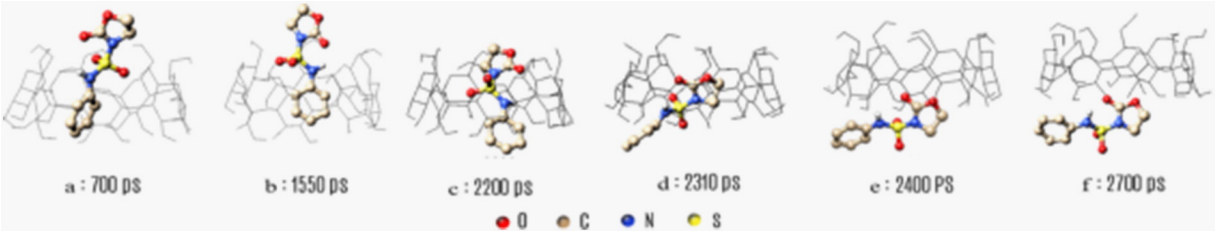

Fig. 3. The geometries of the ONPOS@β-CD complex.

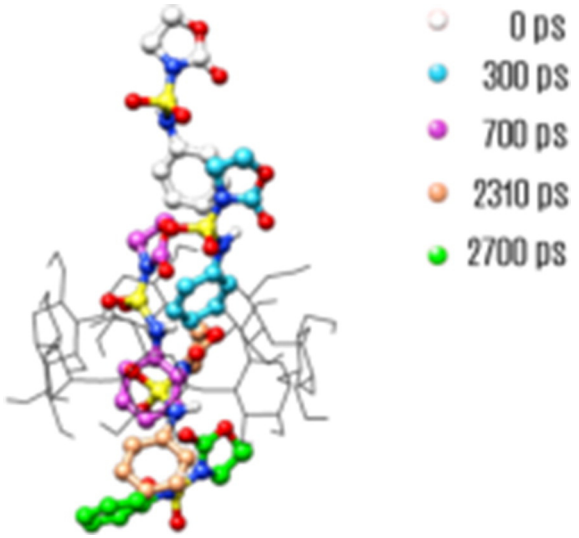

Fig. 4. The evolution of the ONPOS structure progression during the simulation.

600 ps with a time step equal of 0.02 under standard conditions of temperature (298 K) and pressure (1 bar). Then, the simulation was carried out during 3 ns.

Six snapshots were extracted from the simulation at 700, 1550, 2200, 2310, 2400 and 2700 ps. A graphical visualization of the molecular hydrophobicity was performed with Sybyl 2.1.1 package.

4. Quantum mechanics

We have followed several steps using SYBYL-X molecular modeling program for generating the optimal geometry of the ONPOS@β-CD complex. Firstly, the β-CD and ONPOS structures were subjected to atomic charge calculation using Gasteiger Hûckel and followed by the geometries optimization using the tripos force field. After that, the conformational space in the cavity called Protomol in which ONPOS should take inside different poses was generated. For creating this Protomol, we used a Threshold value equal to 0.5 and a value of 0 for Bloats parameters corresponding to a volume of 60 × 63 × 50 Å. This volume can enclose perfectly the ONPOS molecule. The program generates 20 poses that would have been evaluated with different scoring functions. The ranking between all the 20 poses has been made using the consensus score function and total score function. Several tests were made for choosing the better pose. Starting from the better pose, we carried out quantum mechanics optimization using the following methods: B3LYP and MPW1PW91 at 6-31G(d) level. Finally, natural bonding orbitals (NBO) calculations were performed using NBO 3.1 program as implemented in the Gaussian 09 package in order to calculate the second order interactions between the filled orbitals of one subsystem and vacant orbitals of another subsystem, which is a measure of the inter-subsystem interactions.

5. Results and discussion

In Fig. 3 are displayed the geometries of the ONPOS@β-CD complex of the six snapshots extracted at 700, 1550, 2200, 2310, 2400 and 2700 ps.

It shows clearly that the relative position of ONPOS during the MD simulation changes significantly compared to the β-CD position. Thus, both of geometries obtained at 700 and 1550 ps are almost similar. The benzene ring and sulfonamide moiety are located inside the cavity whereas the oxazolidone moiety stays completely outside. However in the geometries obtained at 2200 ps and 2310, the benzene ring is largely situated outside the cavity on the side of the secondary phase, whereas the oxazolidone moiety remains on the periphery of the primary phase. At 2400 and 2700 ps of the simulation, the benzene ring is completely located outside the cavity, whereas the rest of the molecule is totally embedded inside the cavity.

For simplicity this study and provide a quantitative overview of the simulation, we have therefore chosen only five representative snapshots extracted at 0, 300, 700, 2310 and 2700 ps. A scheme of the general overview of the simulation consisting of these snapshots is shown

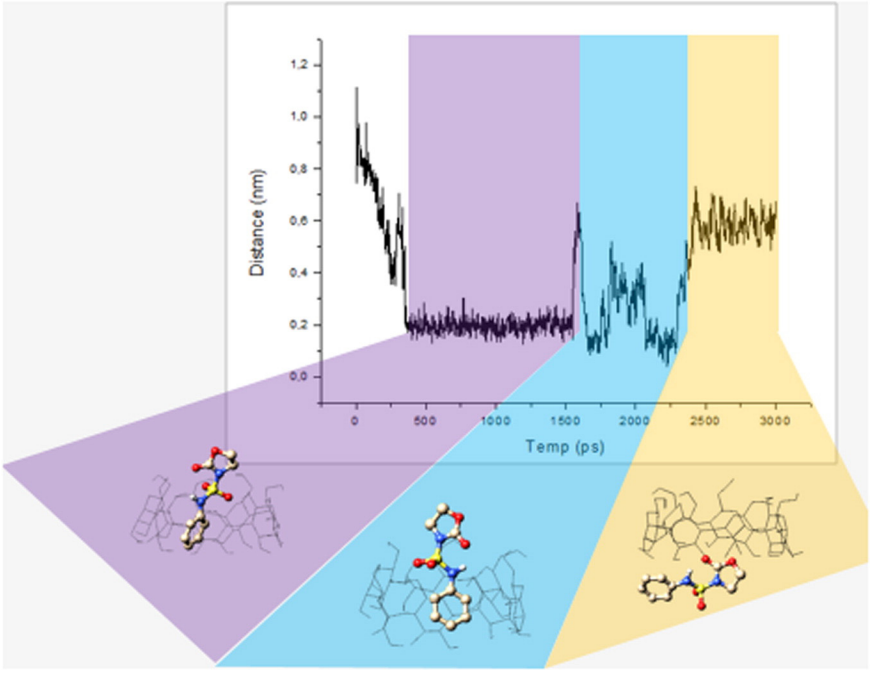

Fig. 5. The variation of the distance between the ONPOS and β-CD centroïds (nm) during the simulation. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

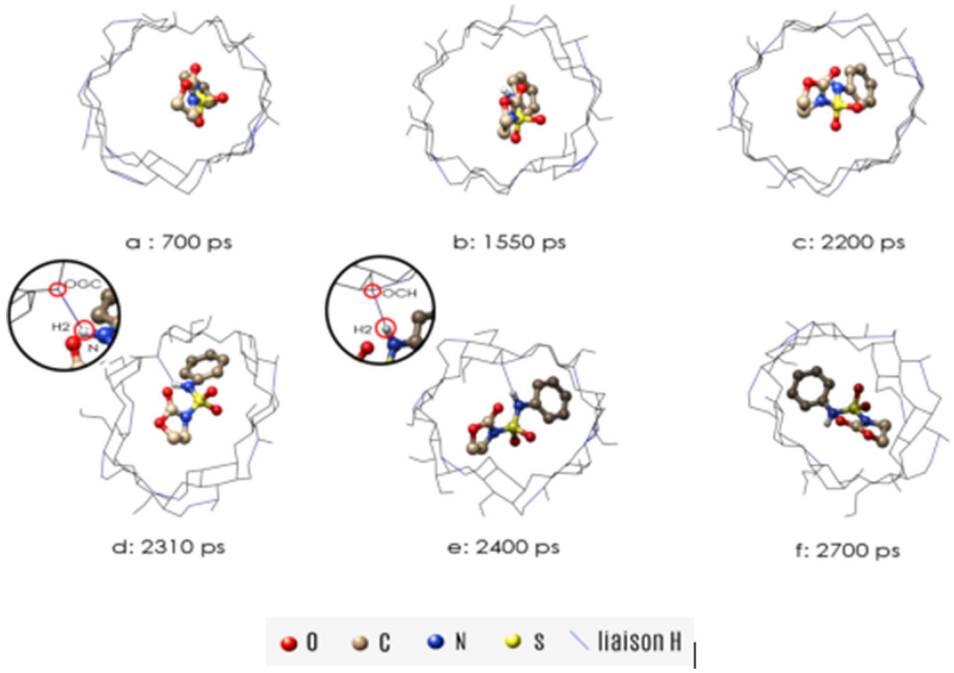

Fig. 6. The formation of hydrogen bond during the simulation.

in Fig. 4, highlighted the displacement of the ONPOS molecule in the box water. As it can be seen, the ONPOS molecule passes through water molecules and arrives in the periphery of the cavity. It penetrates inside and brought out water molecules outside the cavity, and stays in it for a while. At the end of the simulation, ONPOS was found completely outside the cavity.

We will discuss that precisely through Fig. 5 where the geometries of the complex of MD simulation are related to the variation curve of the distance between the two centroïds of ONPOS and β-CD.

As it can be seen, the simulation of the complexation process can be divided into three steps. The first step is ranging from 300 to 1550 ps (purple), the second one of 1550 to 2200 ps (green) and the last one is ranging from 2200 to 3000 ps (yellow).

The following paragraph describes briefly the behavior of ONPOS in the three steps of the complexation process. The first step lasts 1 ns in which the ONPOS molecule is observed throughout the step inside the β-CD cavity forming a stable inclusion complex. The mean distance between the two centroïds is equal to 0.2 nm. The second step lasts 0.5 ns; although the distances between the two centroïds become more important, ONPOS molecule remains in the β-CD cavity. Lastly, the inclusion doesn't occur in the third step and the ONPOS molecule is located outside the cavity with a mean distance between the two centroïds equal to 0.6 nm.

6. Hydrogen bonding interaction

The geometries of the complexes displayed in Fig. 6 shows that hydrogen bond interactions are observed only in both of snapshots extracted at 2310 and 2400 ps; which corresponds to a period without forming an inclusion complex. The first hydrogen bond appeared just at the beginning of the third step of the simulation when ONPOS started to get out the cavity; it was established between a hydrogen atom of the amide group and the glycosidic oxygen (OCC). The second one appears at 2400 ps when ONPOS is completely outside; it was established between the same hydrogen atom of the amide group and the glycosidic oxygen atom (OCH) (Fig. 6).

7. Hydrophobic interaction

The different hydrophobic potentials of the ONPOS@β-CD complex are displayed in Fig. 7; for better visibility, two views have been represented by the primary and secondary phase of β-CD. The analysis of the hydrophobic interaction between β-CD and ONPOS will be based on the partition coefficient Log P, which is distributed across the molecular system in which each atom will have its specific contribution. The color ranges from brown (highest lipophilic area) of the molecule to blue (highest hydrophilic area). The color scheme is easy to interpret

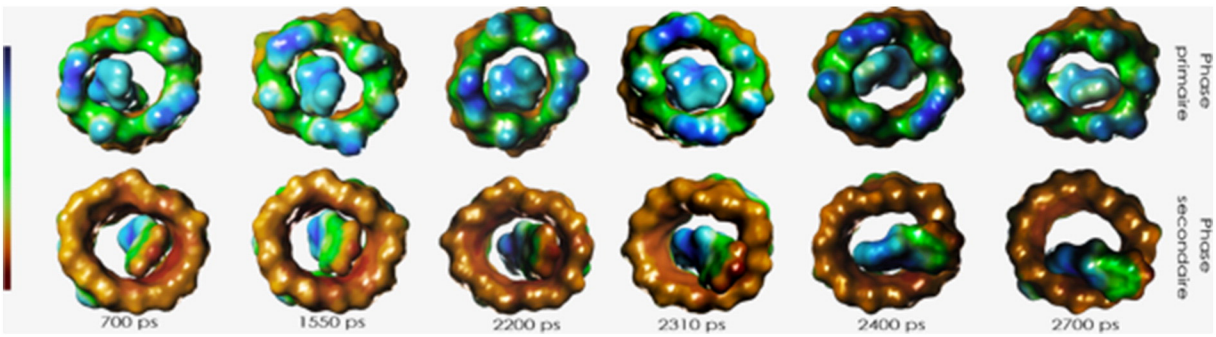

Fig. 7. The scheme color of the hydrophobic potential. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

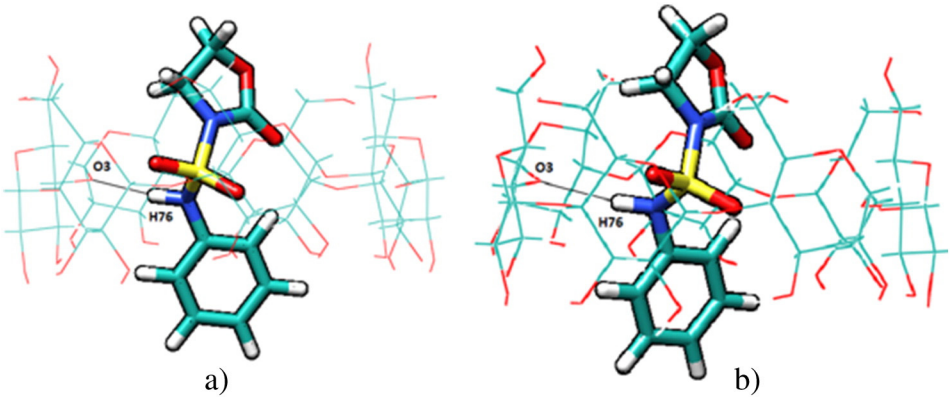

Fig. 8. Geometrical structures optimized with. (a) B3LYP (b) MPW1PW91.

if you associate the blue with water and the brown as oil/fat. Thus, the interaction between ONPOS and β-CD is considered as a hydrophobic favorable interaction when both of colors are similar; whereas the interaction is considered as an unfavorable hydrophobic interaction when the colors are different. A scale on the left of the figure shows the relation between the color and the hydrophobicity values [24].

We will focus only in the first four geometries in which the inclusion phenomenon is observed (700, 1550, 2200 and 2310 ps). They clearly show, as well as in the primary phase (blue-blue) or in the secondary phase (brown-brown) the presence of an interaction between ONPOS and β-CD with the same colors; which means that the inclusion complexation is assisted by favorable hydrophobic interactions. Then, we can say, in molecular dynamics, the most important driving forces are hydrophobic interactions, whereas hydrogen's bondings are not.

8. A quantum mechanics calculation

The geometrical structures optimized with B3LYP and MPW1PW91 at 6-31G(d) level are displayed in Fig. 8 and are found to be almost identical with a perfect inclusion of the ONPOS molecule where only some covalent bonds remain outside the cavity. We note also the establishment of one H-bond between the hydrogen atom H_{76} of NH group and an oxygen atom O_3 of the β-CD.

The following NBO calculation and geometrical data indicated in Table 1 confirm the establishment of the N_{154}—H_{76}···O_{45} hydrogen bond.

These values are typical of standard hydrogen bond in which the energy is between 1 and 5 kcal.mol^{-1}, distance (H_{76}···O_3) < 2.5 Å and angle (N—H_{76}—O_3) > 145°. In both models, the existence of hydrogen bond interaction with a significant energy, equal to 3.63 (B3LYP) and 4.32 (MPW1PW91) kcal.mol^{-1} suggests that H-bond can be considered as one of the driving force of the complexation.

However, the scheme color (Fig. 9) of the hydrophobicity potential of the ONPOS@β-CD complex shows an unfavorable hydrophobic interaction in primary phase displayed in the left side (brown-blue) and a favorable hydrophobic interaction in the secondary phase displayed on the right side (brown-brown).

In the quantum mechanics study, it appears that the hydrogen bonding interaction is the most important driving forces, whereas the hydrophobicity interaction has only a partial influence on the formation of the ONPOS@β-CD complex.

Table 1
$E^{(2)}$ energy, the distance and the angle of the N_{154}—H_{76}···O_3 hydrogen bond.

H-bond	Distance (Å)		Angle (°)		$E_{(2)}$ (kcal.mol$_{-1}$)	
	B3LYP	MPW1PW91	B3LYP	MPW1PW91	B3LYP	MPW1PW91
N—H_{76}···O_3	2.3	2.2	164	166	3.63	4.32

9. Conclusion

The complexation process of ONPOS with β-CD has been studied using molecular dynamics and quantum mechanics with the aim to determine the driving forces of the inclusion. Hydrogen bonding interaction was quantified using NBO method and the hydrophobicity interaction is highlighted using a scheme color of the potential surface of hydrophobicity in the molecular structure. Thus, MD simulation results show that hydrophobic interaction is the most driving force in the complexation whereas the hydrogen bonding interaction doesn't contribute at all. These results are certainly due to the high sensitivity of MD simulation to the hydrophobicity-hydrophilicity of the medium because of the large number of water molecules. Also, it was seen ONPOS tends to get out the cavity at the end of the simulation; this

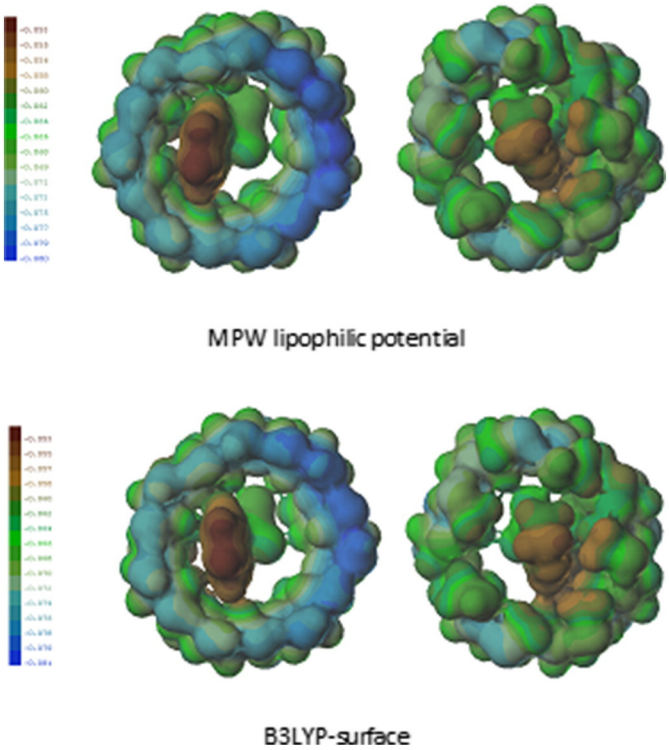

Fig 9. The lipophilic potential of the ONPOS@β-CD complex. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

expected behavior is due to the attraction of the hydrophilic extremity of the ONPOS molecule by the great number of hydrophilic water molecules. On the contrary, using DFT (B3LYP and MPW1PW91) quantum mechanics have shown that the most driving force of the complexation corresponds to the hydrogen bonding interaction. However, the hydrophobicity interaction has only a partial influence in the formation of ONPOS@β-CD complex. However, for QM calculations, which are performed only on its lowest energy minimum, the results show that QM method is rather more sensitive to the interactions between pairs of electrons of ONPOS and β CD molecules leading to the establishment of intermolecular hydrogen bonds. Further studies on the explicit role of water molecules in the dynamic of the inclusion process are under studies in our groups.

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