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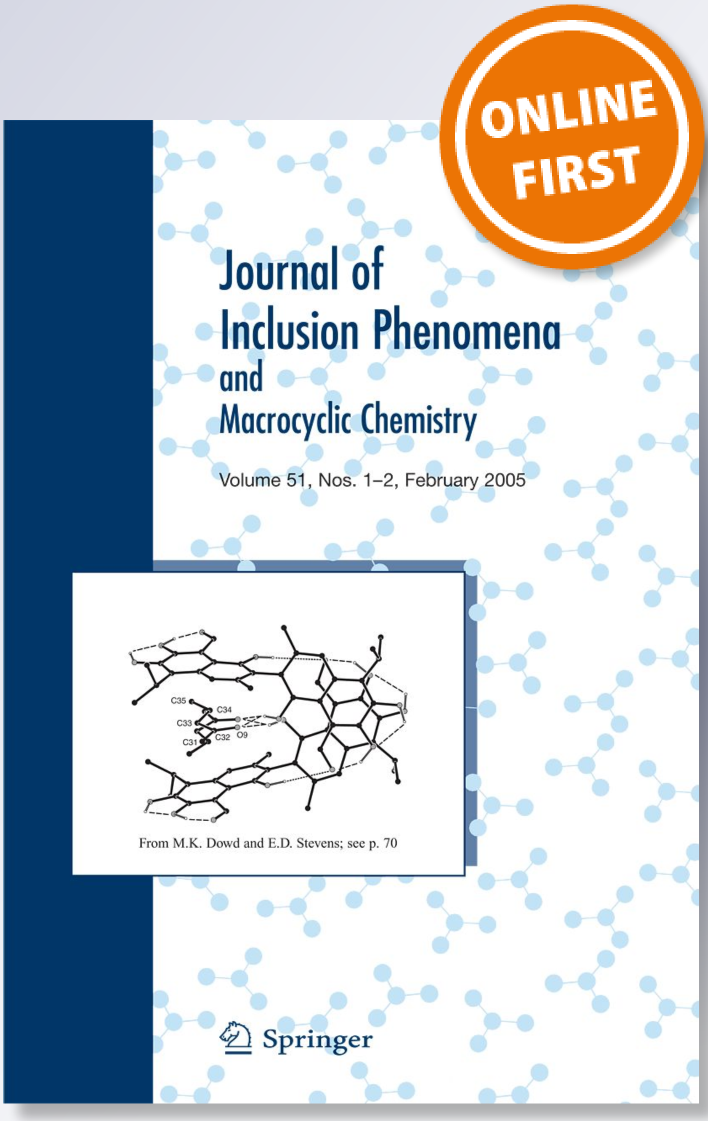

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ORIGINAL ARTICLE

Theoretical investigation study based on PM3MM and ONIOM2 calculations of β-Cyclodextrin complexes with diphenylamine

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Abstract The inclusion complex of β-cyclodextrin (β-CD) and diphenylamine (DPA) was investigated by using PM3MM, DFT, HF and ONIOM2 methods. The most stable structure was obtained at the optimum position and angle. The results indicate that the inclusion complex formed by DPA entering into the cavity of β-CD from its wide side (the secondary hydroxyl group side) is more stable than that formed by DPA entering into the cavity of β-CD from its narrow side (the primary hydroxyl group side). The structures show the presence of several intermolecular hydrogen bond interactions that were studied on the basis of natural bonding orbital (NBO) analysis, employed to quantify the donor–acceptor interactions between diphenylamine and β-CD. A study of these complexes in solution was carried out using the CPCM model to examine the influence of solvation on the stability of the diphenylamine β-CD complex.

Keywords Diphenylamine · β-CD · PM3MM · ONIOM2 · NBO

Introduction

The study of inclusion complexes of organic molecules with cyclodextrins (CDs) has attracted the interest of many experimental and theoretical chemists during the past decades [1, 2].

CDs (Fig. 1) are cyclic oligosaccharides obtained by the enzymatic degradation of starch. They are formed by the association of six, seven or eight units of glycopyranose linked by a (1, 4) connections and named respectively α, β and γ-CD. They bear hydrophobic cavities capable of forming inclusion complexes with a variety of organic molecules. CDs are known for their ability to bind organic molecules by noncovalent interactions and it has been reported that the hydrophobic effects, van der Waals interactions, dipole dipole interactions and charge transfer interactions are the possible driving forces for the inclusion complex [3]. In particular, β-cyclodextrin (β-CD) has an internal cavity shaped like a truncated cone of about 8 Å deep and 6.0–6.4 Å in diameter. This cavity possesses a relatively low polarity, so it can accommodate guest organic molecules inside [4]. By this means, β-CD can improve the stability, dispersing and dissolving properties of some drugs, and enhance its physical and chemical activity through the inclusion complexes [5]. Therefore, β-CD is by far the most widely used in pharmaceutical sciences and different fields of chemistry ranging from analytical to synthetic chemistry in CDs [6, 7].

DPA, as a guest molecule, could be easily encapsulated inside β-CD to form 1:1 inclusion complexes.

Experimental results reported by R. Rajamohan and Swaminathana [8] that the ratio between β-CD and DPA complex is of 1:1 type, and our calculation indicate that β-CD and DPA can form 1:1 inclusion complex. This inclusion complex formation from DPA and β–CD was, revealed by UV and confirmed by the FT-IR spectral study and SEM image analysis. In continuation of the work of R. Rajamohan and Swaminathana [8], the current study examines the detailed inclusion complexation of DPA and β-CD by means of PM3MM, DFT, HF and ONIOM2 methods.

B. Abdelaziz · N. Leila (✉) · H. Sakina · D. Imene ·
M. Fatiha · K. DjamelEddine
Laboratory of Computational Chemistry and Nanostructures,
Department of Material Sciences, Faculty of Mathematical,
Informatics and Material Sciences, University of 08 Mai 1945,
Guelma, Algeria
e-mail: leilanoua@yahoo.fr

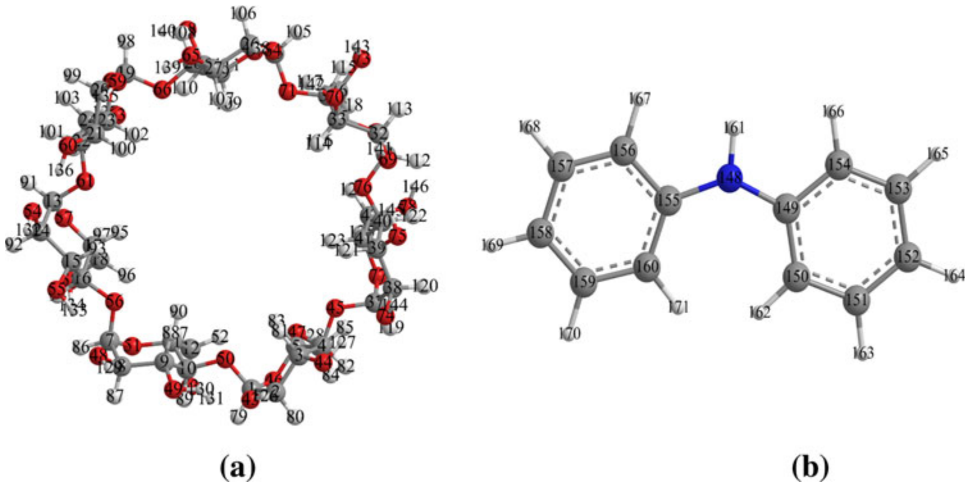


Fig. 1 Geometrical structures of β-CD (**a**) and diphenylamine (**b**) optimized at PM3MM method

In the last decade, quantum chemical computations have become an established method for the prediction of novel structures and properties and are now being used widely to support experimental work. As such, they could provide a powerful tool for the rotational design of supramolecular systems and inclusion phenomena. Computations using semi-empirical, ONIOM2 and quantum me chemical methods are currently fast enough to make studies of supramolecular and inclusion systems feasible. [9–21].

In the present paper, we describe the structures of DPA/β-CD inclusion complex as obtained from PM3MM as well as (MPW1PW91/6-31G (d):PM3MM), (M05-2X/6-31G (d):PM3MM) and (B3LYP/6- 31G (d):PM3MM) ONIOM2 calculations, in order to approach the ideal geometry and provide further insight of the complexation process of DPA with β-CD.

Computational details

All calculations were performed using Gaussian 09 program [22]. The structure of DPA was constructed using Hyperchem 7.5 molecular modeling package [23]. The starting geometry of β-CD was taken from Chem-Office 3D ultra (version10, Cambridge software). Then the two structures DPA and β-CD were optimized by PM3MM semi-empirical method. The method used by Liu and Guo was employed [24]. The glycosidic oxygen atoms of β-CD are placed in XY plane and their center is defined as the center of the whole system. DPA approaches and passes through the cavity of β-CD from +Z to −Z direction, and the distance between the labeled atom N of DPA and β-CD ranges from −12 to +12 Å. The guest is initially located at a Z-coordinate of 12 Å and is moved through the host cavity along the Z-axis to −12 Å at with a stepwise 1 Å. For each step, the geometry of the complex is fully optimized by PM3MM without imposing any symmetrical restrictions. In order to find an even more stable structure of the complex, each guest molecule is calculated for all of the structures obtained by scanning θ, clockwise circling around Z-axis, at 30° intervals from 0° to 360°. PM3MM semi-empirical method was firstly used to study the complexation process as describe above. The solvent effects on the conformational equilibrium have been investigated using the PCM model for water ($\varepsilon = 78.39$) as a solvent with PM3MM method. For the equilibrium geometries of the DPA/β-CD complexes, DFT or ab initio HF single point calculations with the split-valence 6-31G(d) basis set were performed for the PM3MM-optimized complexes both in vacuum and in water solution.

Two possible orientations of the guest molecule in complex were considered. The orientation in which the DPA points toward secondary hydroxyl of β-CD was called the "A model", the other, in which the guest points toward the primary hydroxyl of β-CD was called the "B model", see Fig. 2.

Several energy expressions were used to characterize the inclusion complexes the binding energy ($BE_{binding}$) is defined as the difference between the energy of the complex and the energy of the individual components in their optimized geometry ($E_{opt,DPA}$ or $E_{opt,CD}$) from the complex,

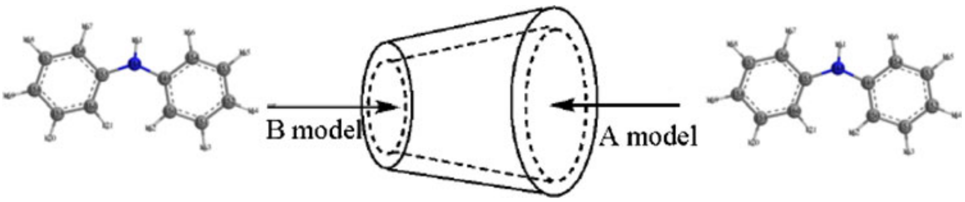
$$BE_{binding} = E_{complex} - (E_{opt,DPA} + E_{opt,CD}) \tag{1}$$

For a deeper understanding of the molecular recognition, the equilibrium geometries of both DPA/β-CD complexes were also completely optimized using the ONIOM (B3LYP/6-31G (d):PM3MM), (M05-2X/6-31G (d):PM3MM) and ONIOM (MPW1PW/6-31G (d):PM3MM). The total ONIOM energy E^{ONIOM} is given by eq 2.

$$E^{ONIOM} = E\,(\text{high; model}) + E\,(\text{low; real}) - E\,(\text{low; model}) \tag{2}$$

where E (high, model) is the energy of the inner layer at the high level of theory (the DPA molecule), E (low, real) is

Fig. 2 The proposed structures of diphenylamine/β-CD complex for *A* and *B* models



the energy of the entire system at the low level of theory (the complexes), and E (low, model) is the energy of the model system at the low level of theory (β -CD).

Finally Charge transfers between host and guest molecules have been studied using the NBO 3.1 program as implemented in the Gaussian 03 W package, calculated with both ONIOM [MPW1PW/6-31G (d)] and ONIOM [B3LYP/6-31G (d):PM3MM] methods in order to understand various second-order interactions between the filled orbital of one subsystem and vacant orbital of another subsystem, which is a measure of the intermolecular delocalization or hyper conjugation.

Results and discussion

Structure of the β-CD/DPA inclusion complex

The analysis of the potential energy surfaces corresponding to this closing-up and rotation of the β-CD/DPA complexes shows several energy minima at different combinations of rotation angles and distances. The optimum position and angle for DPA into β-CD at A model and B model can be, respectively, determined according to the binding energy. Other possible locations and angles of DPA were examined using the PM3MM method, but were shown to be energetically less favorable and so they were not listed.

Passing process

Figure 3 depicts BE for the approach of DPA to β-CD with A and B models. The complexation process is energetically favorable. The most stable structure is reached at approximately Z = 3A° and Z = 4 A° for the A model and the B model approaches, respectively. The negative BE changes demonstrate that β-CD can form a stable complex with DPA, and the changes are similar to the reports for MM studies on CD systems [25].

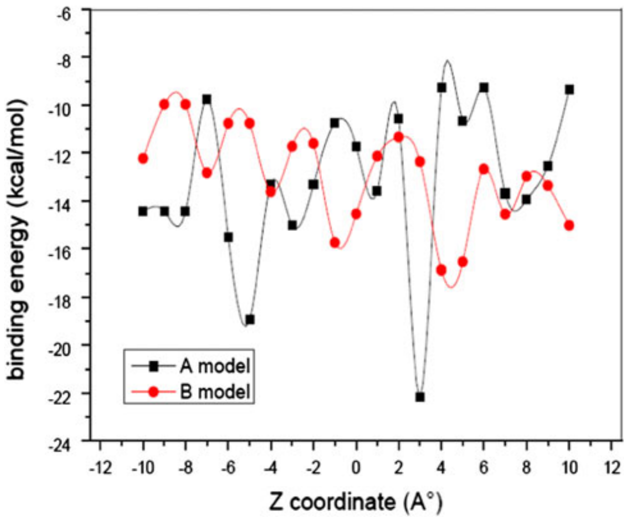


Fig. 3 Stability energies of the inclusion complexation of diphenylamine into β-CD at different positions, PM3MM calculations

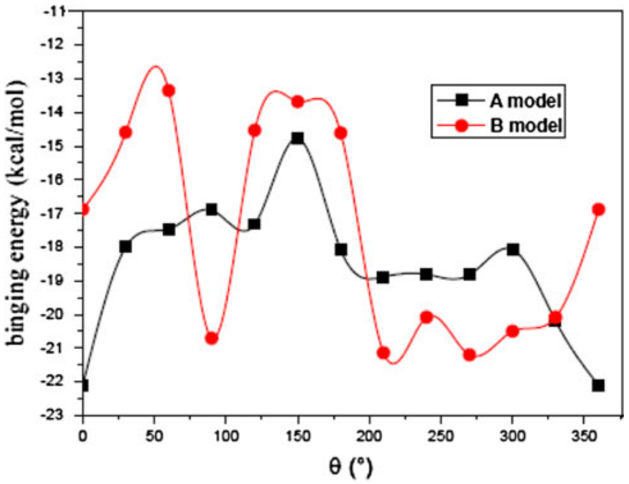


Fig. 4 Stability energies of the inclusion complexation of diphenylamine into β-CD at different scanning θ, PM3MM calculations

Circling process

It should be pointed that the initial structures studied in circling process are the most stables complexes obtained in the passing process. Thus, in circling process, DPA is placed in XY plane and rotated around Z-axis, by 30° from 0° to 360°. The energy changes of A and B models are exhibited in Fig. 4. As we can see from Fig. 4, the energy undulate in certain scope which ranges respectively from −14, 76 to −22.23 kcal/mol in A model and from −3.35 to −21, 14 kcal/mol in B model. We can also notice that the lowest energy is obtained when θ is equal to 0° for A model and to 270° for B model.

The structures of the energy minimum in the A and B models obtained with PM3MM optimization are shown in

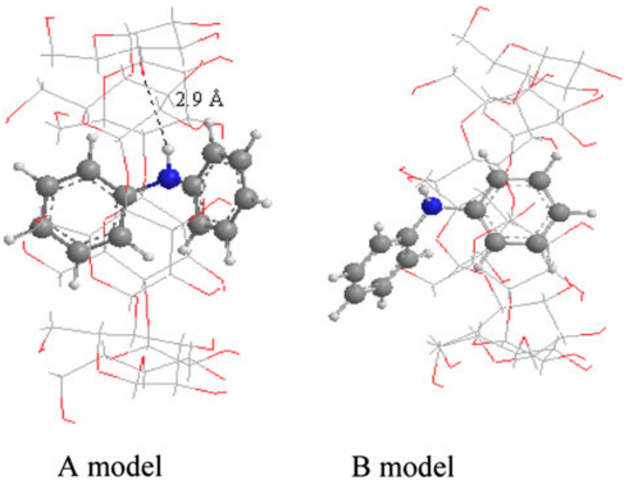


Fig. 5 Structures of the energy minimum obtained by the PM3MM calculations

Fig. 5. For A model, the guest is totally encapsulated in β-CD cavity. The structural analysis of A model show the presence of one hydrogen bonds formed between hydrogen atom H (161) of amine group NH of DPA and oxygen atom O (56) interglycosidic of β-CD with a distance of 2.9 Å. (See Fig. 5). In the case of B model no H–bond was found and the guest molecule is partially encapsulated in β-CD cavity, this explains why the binding energy of the inclusion in the model A is lower than that of the model B.

The calculated binding energy for DPA/β-CD for A and B models with and without solvents are mentioned in Table 1.

The binding energies in vacuum were found equal to −22.23 kcal/mol for A model and to −16.85 kcal/mol for B model; corresponding to a difference between the two models equal to 5.38 kcal/mol. Generally, the complex with more negative binding energy is considered the most

Table 1 Energies (kcal/mol) and dipole moments (Debye) at PM3MM calculations in vacuum and in water

	DPA	β-CD	A model	B model
PM3MM				
E (Kcal/mol)	56.84	−1449.15	−1414.54	−1409.16
BE (Kcal/mol)			−22.23	−16.85
E_{HOMO} (eV)	−10.1	−10.621	−10.55	−10.428
E_{LUMO} (eV)	−0.441	18.352	−1.065	−1.086
(E_{HOMO}-E_{LUMO}) (eV)	−9.659	−28.973	−9.485	−9.342
μ (D)	1.39	3.73	2.57	5.77
In vacuum				
B3LYP/6-31G (d)				
E (Kcal/mol)	−323677.13	−2667956.18	−2991629.05	−2991586.71
BE (Kcal/mol)			4.26	46.6
Mpw1pw91/6-31G (d)				
E (Kcal/mol)	−323599.25	−2667372.10	−2990966.90	−2990926.08
BE (Kcal/mol)			4.45	45.27
HF/6-31G(d)				
E (Kcal/mol)	−321538.36	−2652913.34	−2974437.01	−2974398.56
BE (Kcal/mol)			14.69	53.14
In water (CPCM model)				
PM3MM				
E (Kcal/mol)	54.79	−1475.22	−1441.93	−1435.72
BE (Kcal/mol)			−21.5	−15.29
B3LYP/6-31G (d)				
E (Kcal/mol)	−323683.32	−2667996.59	−2991672.97	−2991627.93
BE (Kcal/mol)			6.94	51.98
Mpw1pw91/6-31G (d)				
E (Kcal/mol)	−323560.69	−2667039.42	−2990587.61	−2990543.55
BE (Kcal/mol)			12.5	56.56
HF/6-31G (d)				
E (Kcal/mol)	−321545.72	−2652965.47	−2974493.73	−2974452.19
BE (Kcal/mol)			17.46	59.00

favored one (A model). The same result is also obtained with the B3LYP/6-31G(d), Mpw1pw91/6-31G(d) and HF/6-31G(d) single point calculation in vacuum in which the energy difference becomes 42.34; 40.82 and 38.45 kcal/mol, respectively. From Table 1, the BE computed in vacuum with the HF and DFT methods is positive, this does not necessarily mean that the complexation is unfavorable, for the large complexed system is optimized at the level of PM3MM but not DFT and HF.

Furthermore, the (E_{HOMO}–E_{LUMO}) gap is an important stability index [26] and chemicals with larger (E_{HOMO}–E_{LUMO}) values tend to have higher stability, so we investigated the electronic structure of the complexes in the two models using PM3MM method. The results are reported in Table 1. In fact, with the increase of the (E_{HOMO}–E_{LUMO}) gap for the complexes formed in the A model, we present a new confirmation that DPA/β-CD inclusion complexes are more stable when the DPA enters the cavity by its large side, which agrees well with the calculated results of the binding energies discussed above.

Compared the dipole moment of the two models in vacuum, we can obtain that the dipole moment of A model is 3.20 D smaller than that of B model, which means that the dipole moment of the complex have a closed relation with the polarity of the guest molecules.

It is well known that generally the formation of the inclusion complexes involving β-CD takes place in aqueous solution; so, the binding behavior of β-CD and DPA in solution seems to be more important than their in vacuum. For this, we under took PM3MM calculations in solutions in order to examine the influence of the solvation effect on the binding energy of the inclusion complexes. The results of calculations listed in Table 1 confirm those obtained in vacuum and the gap energetic between the two models obtained with PM3MM (6.21 kcal/mol) is increased using single point calculations at B3LYP/6-31G(d), Mpw1pw91/6-31G(d) and HF/6-31G(d) level and confirm the preference for A model with 45.04, 44.06 and 41.54 kcal/mol respectively.

Geometrical parameters

We report, in Table 2, the selected geometrical parameters such the bond distances and the most interesting dihedral angles for free and encapsulated DPA molecule before and after complexation as calculated by PM3MM methods for the most stable structures in A and B models. It is evident that in β-CD, the geometry of DPA is completely altered. The alteration is significant in dihedral angles, which, indicates that DPA must adapt a specific conformation to form a more stable inclusion complex.

The geometrical changes of β-CD before and after complexation with diphenylamine, calculated by PM3MM method are shown in Table 3. We note that the interactions

Table 2 Geometrical parameters of DPA before and after inclusion in β-CD, bond distances (Å) and dihedral angles (°) calculate PM3MM methods

	Free DPA	A model	B model
Bond lengths (Å)			
N_{148}–H_{161}	1.01	1.01	1.01
N_{148}–C_{155}	1.40	1.39	1.38
C_{155}–C_{156}	1.41	1.40	1.40
C_{157}–C_{158}	1.41	1.40	1.40
C_{159}–C_{160}	1.40	1.39	1.39
C_{148}–C_{149}	1.40	1.39	1.39
C_{149}–C_{150}	1.41	1.40	1.40
C_{149}–C_{154}	1.41	1.40	1.40
C_{152}–C_{153}	1.40	1.39	1.39
Dihedral angle (°)			
C_{156}–C_{155}–N_{148}–C_{149}	180	152.49	152.807
C_{148}–C_{155}–C_{160}–C_{159}	0	−178.071	−178.045
C_{148}–C_{149}–C_{154}–C_{153}	180	0.652268	0.674386
C_{148}–N_{149}–C_{150}–C_{151}	180	170.42	169.127
H_{161}–N_{148}–C_{155}–C_{160}	180	157.92	156.545
H_{161}–N_{148}–C_{149}–C_{150}	180	160.18	159.689

Table 3 Distances (Å) in β -CD before and after complexation with diphenylamine, calculated by PM3MM methods

	Free β –CD	β-CD in A model	β-CD in B model
Primary hydroxyls			
O53–O47	4.221	4.676	3.533
O47–O78	6.056	6.237	6.286
O78–O73	5.548	6.448	5.287
O73–O68	6.258	5.407	7.748
O68–O63	4.126	4.857	3.443
O63–O58	6.07	6.08	6.217
O58–O53	5.65	5.777	7.385
Secondary hydroxyls			
O74–O43	5.613	5.568	5.607
O43–O48	5.60	5.575	5.954
O48–O54	5.598	5.605	6.04
O54–O59	5.615	5.591	5.529
O59–O64	5.591	5.582	5.989
O64–O69	5.604	5.596	6.043
O69–O74	5.591	5.606	5.976
The glycosidic oxygen atoms			
O76–O71	4.229	4.529	4.139
O71–O66	4.44	4.301	4.235
O66–O61	4.293	4.295	4.329
O61–O56	4.391	4.420	4.175
O56–O50	4.407	4.409	4.364
O50–O45	4.2893	4.31	4.268
O45–O76	4.429	4.265	4.383

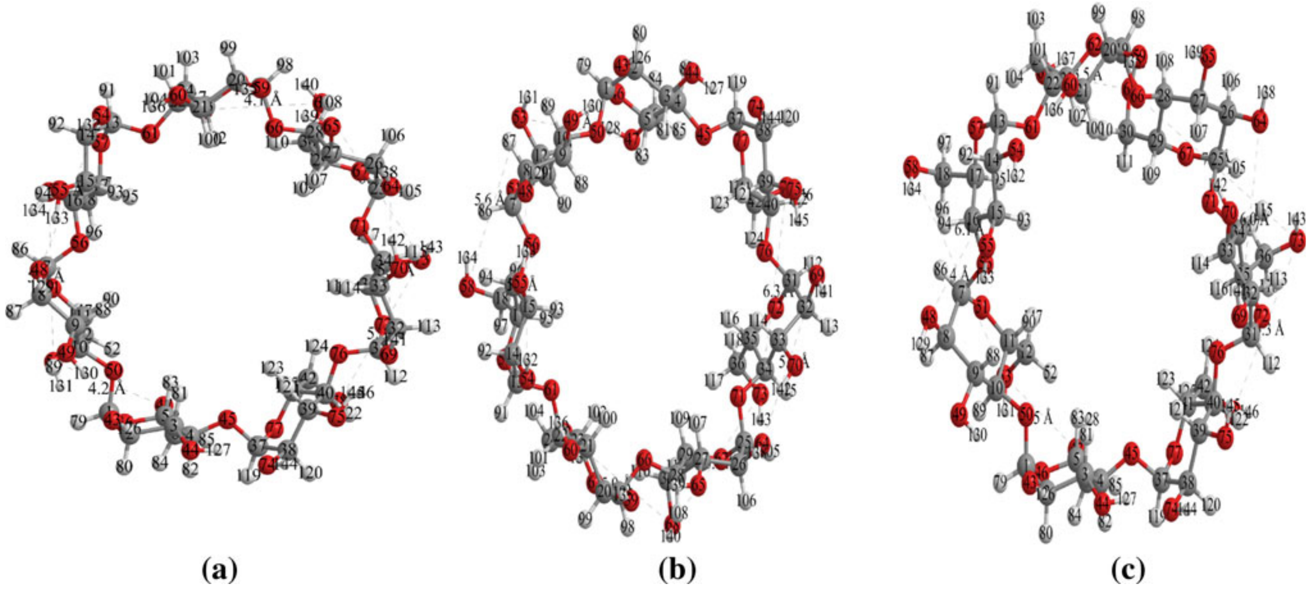


Fig. 6 PM3MM optimized structure of β -CD (**a**) and structure of β -CD after guest inclusion (**b**, **c**). **b, c** are the A and B models respectively after removal of the structure of the DPA. The *dotted lines length* represents the distance between numbered atoms

between diphenylamine and β-CD leads to significant distortion of the host cavity compared to the isolated β-CD. The geometrical changes of β-CD after guest inclusion are shown in Fig. 6a, b, c). The round cavity (Fig. 6a) of β-CD turns into an oval shaped cavity (Fig. 6b, c). Atoms O48–O54 and O64–O69 are part of the hydroxyl groups of the top rim of β-CD. Atoms O53–O47, O78–O73, O73–O68, O68–O63 and O58–O53 are the part of the hydroxyl groups of bottom rim of β-CD. For The glycosidic oxygen atoms the distortion of CD is less. Therefore, the hydroxyl groups of the top/bottom and the glycosidic oxygen of the rim of β-CD play a significant role in binding the DPA.

Table 4 Relative energy for the optimized structures of complexes DPA/β-CD in both models as calculated by ONIOM2 method

	A model	B model	ΔE
E (PM3MM)	−1414.54	−1409.16	−5.38
E^{ONIOM} (B3LYP/6-31G(d):PM3MM)	−326929.01	−326924.83	−4.18
E^{ONIOM} (mpw1pw91/6-31G(d):PM3MM)	−326853.34	−326849.25	−4.09
E^{ONIOM} (M05-2X/6-31G(d):PM3MM)	−326893.31	−326888.67	−4.64

ΔE is relative energy difference, ΔE = E (A model) − E (B model)

ONIOM calculation

In our hybrid model study, we submitted the host molecule β-CD to the low level of quantum calculations (PM3MM) since we assumed it provides only an environmental effect and contains the larger number of atoms, while the guest molecule DPA is treated at a high level of calculation at a medium basis set corresponding to B3LYP/6-31G (d), M05-2X/6-31G (d) and MPW1PW91/6-31G (d). In Table 4, we reported and compared the energetic values computed with ONIOM2 method to those obtained from PM3MM calculations. We found that the ONIOM calculations confirm PM3MM results. In fact both ONIOM2 ((B3LYP/6-31G (d):PM3MM)), ONIOM2 (Mpw1pw91/6-31G (d):PM3MM) and ONIOM2 (M05-2X/6-31G (d):PM3MM) predicted A model to be more favorable than B model by respectively −4.18, −4.09 and −4.64 kcal/mol. The relative energy difference of the optimized complexes has the same order of magnitude than that obtained by PM3MM method.

Considering the binding energy, we can conclude that ONIOM2 (M05-2X/6-31G (d): PM3MM), offers the closest value of the PM3MM method.

NBO analysis

The natural bonding orbital (NBO) analysis was applied for investigating donor–acceptor interactions in the complexes of DFA with β-cyclodextrin. Table 5 shows some of the significant donor–acceptor interactions and their stabilization energies $E^{(2)}$.

It is clear from Table 5 that mainly σ-C–H of DPA plays an important role of electron donation to the vacant σ*-C–H orbital of β-CD. On the other hand, β-CD shows electron donation from C of glucosidic units to σ*-C–H vacant orbital of DPA. The obtained stabilization energies

Table 5 Donor–acceptor interactions and stabilization energies $E^{(2)}$ (kcal/mol)

Donor	Acceptor	$E^{(2)}$ B3LYP/ 6-31G(d)	$E^{(2)}$ MPW1PM91/ 6-31G(d)
A model			
σ (1) C 15–H 93	σ*(1) C 154–H 166	2.78	2.72
σ (1) C 17–H 95	σ* (1) N 148–H 161	2.13	2.12
σ (1) C 17–H 95	σ*(1) C 156–H 167	1.38	1.35
σ (1) C 41–H 123	σ*(1) C 159–H 170	2.88	2.82
LP (1) O61	σ*(1) N148- H 161	1.32	1.30
Total		10.49	10.31
B model			
σ (1) C 12–H 147	σ*(1) N 148–H 161	4.40	4.36
σ (1) C 15–H 93	σ*(1) C 157–H 168	2.45	2.43
σ (1) C 33–H 114	σ*(1) C 159–H 170	2.50	2.52
σ (1) C 41–H 123	σ*(1) C 160–H 171	1.81	1.80
Total		11.16	11.11

$E^{(2)}$ from B3LYP/6-31G(d) were 10.49 and 11.16 kcal/mol for A and B models respectively. For MPW1PM91 results, the stabilization energies were 10.31 and 11.11 kcal/mol for A and B models respectively. Thus, the encapsulation of DPA with β-CD for A model is less demanding in energy than B one.

Conclusion

The stable structures and the inclusion process for DPA/β-CD inclusion complexes were studied by use of PM3MM, DFT, HF and ONIOM2 methods according two models. The minimum energy structure for each model was localized with the PM3MM method. The DPA guest molecule is enwrapped into the cavity of β-CD, and the inclusion complex formed by DPA entering into the cavity of β-CD from its wide side (the secondary hydroxyl group side) is more stable than that formed by DPA entering into the cavity of β-CD from its narrow side (the primary hydroxyl group side). This result is completely similar to that obtained from HF, DFT and ONIOM2 calculations. To form stable inclusion complex, the conformation of DPA is significantly altered during complexation. The NBO natural bonding orbital population analysis used to quantify the interaction between DPA and β-CD show that the driving forces of DPA–β-CD complexes was due to the intermolecular hydrogen bonds in addition to the hydrophobic interactions. The study in solution by using CPCM model follows the same trend as that in vaccuo, thus favoring the A model.

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