

Full Paper

## Molecular modeling study of para amino benzoic acids recognition by $\beta$ -cyclodextrin

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Received: 11 August 2008; revised: 16 October 2008; accepted: 07 November 2008.  
Available online: 25 January 2009.

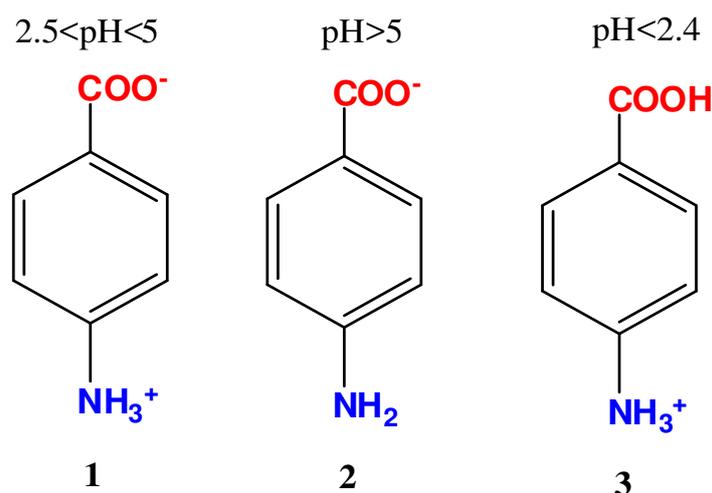
**ABSTRACT:** AM1 and PM3 methods were applied to investigate equilibrium geometries of inclusion complexes formed between  $\beta$ -CD and neutral, anionic and cationic species of PABA (Para amino benzoic acid).  $\beta$ -CD can bind to these three species (two possible orientations A or B) with negative binding energy, where the preference between A and B orientation of each PABA species is due to H-bond interaction. Finally, the HOMO and LUMO energies of each complex were calculated and compared.

**Keywords:** PABA, cyclodextrin, inclusion complex, PM3, AM1, B3LYP/6-31G\*

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## Introduction

Para-aminobenzoic acid (PABA) is an isomeric form of amino benzoic acid (ABA) that is often thought as only an ingredient used in sunscreens preparations since it can help protect the skin against ultra-violet radiation, while it is in actual fact a nutritional ingredient as well [1, 2]. Since it is a moiety of PGA, a form of folic acid, some health professionals do not consider it a vitamin, but only a B-complex factor. PABA is promoted as a dietary supplement that has properties that include improving the metabolism of amino acids, improving the formation and health of blood cells, it relates to red blood cell formation as well as assisting the manufacture of folic acid in the intestines [3, 4]. The PABA can exist in three forms (neutral, anion and cation) according to the pH of the environment (see Scheme 1). PABA application is limited because it has a lower emission of fluorescence and it can damage DNA after UV irradiation. To avoid these effects PABA was used as a complexed form in cyclodextrins (CDs). This inclusion can increase aqueous solubility and fluorescence emission.

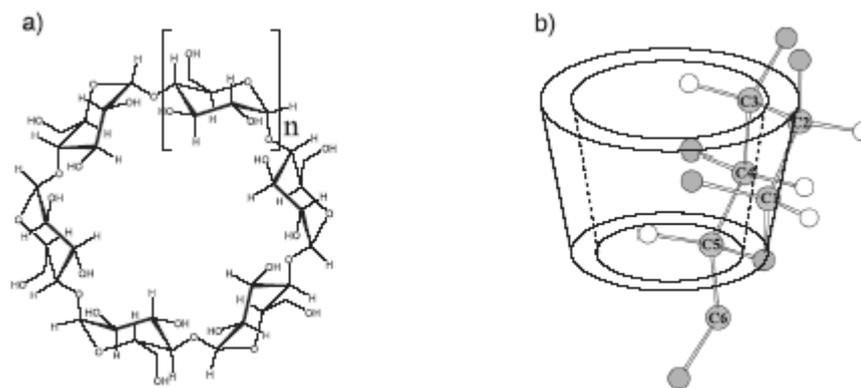


**Scheme 1.** Species form of PABA at different pH values

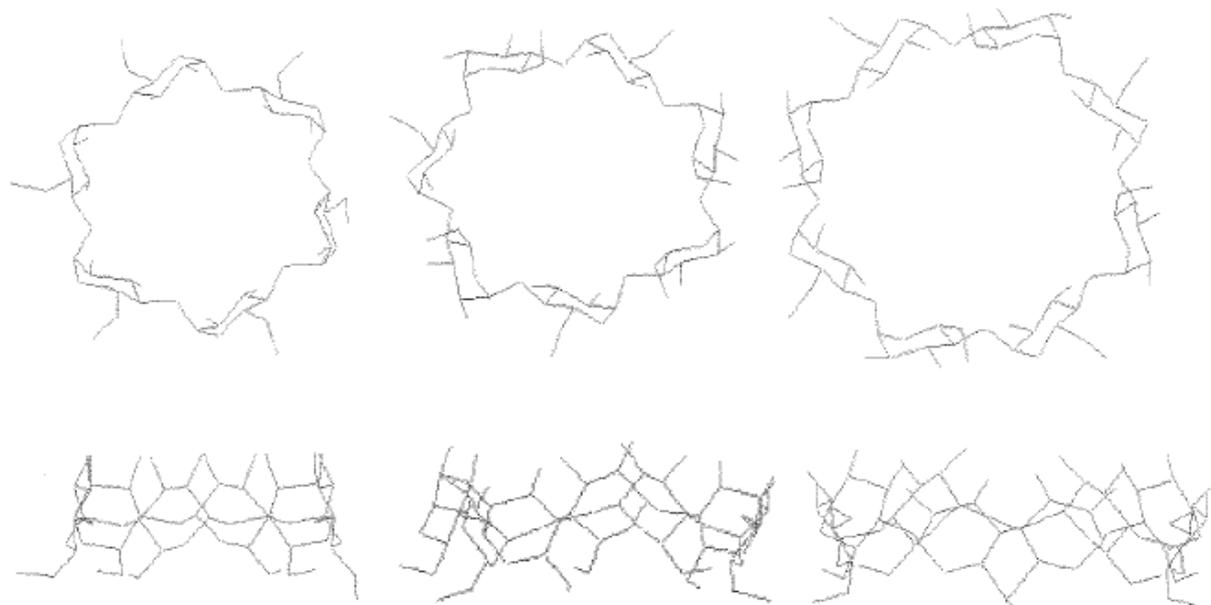
Cyclodextrins are well-known sugar oligomer built up from glucopyranose units (see Scheme 2). Each unit is bonded to the other through  $\alpha$ -1,4-glycosidic linkage and hence the units together form a cyclic ring of doughnut or wreath-shaped truncated cone [5].

The most widely used cyclodextrins are alpha, beta, and gamma cyclodextrins consisting of 6, 7 and 8 units, respectively (see Scheme 3). These cyclodextrins have a hydrophilic outside and hydrophobic cavity surrounded by glycosidic units. This cavity allows the cyclodextrins to include different guest molecules (organic, inorganic etc.) with different stoichiometry depending on the size of the guest molecule [6]. Thus, the

presence of asymmetric carbon in the glycosidic units offered the CDs owned by recognizing and separating enantiomers.



**Scheme 2.** Top view of a)  $\beta$ -cyclodextrin b) glycopyranos unit.



**Scheme 3.** Molecular geometries of  $\alpha$ ,  $\beta$ , and  $\gamma$  cyclodextrin.

Encapsulation in cyclodextrins helps to protect fragile molecules, increase the solubility of hydrophobic molecules and alter some properties of guest molecules [7-10].

Cyclodextrins have a cavity from approximately 5 to 8 Å of diameter which enables them to include many organic compounds to form inclusion complexes in a solid state or in solution. Using the three-dimensional structures of X-rays the truncated shape of cyclodextrins could be given, as well as the network of secondary hydrogen

bonds. On the largest part of the cone are positioned the secondary hydroxyls (O2 and O3) and on the narrowest end are positioned the primary hydroxyls (O6). Oxygens interglycosidic (O4) are located on the equator of the cone and are directed towards the interior of the cavity. Hydrogen H1, H2 and H4 are directed towards the outside of the cavity while hydrogen H3 and H5 are directed towards outside. These latter are only being able to interact with a substrate included in the cavity. Due to of the truncated structure and the position of hydroxyls, the cyclodextrins are amphiphilic and thus have two zones of distinct polarities. The outside of the cavity and the ends are polar: this is due primarily at the hydroxyls and thus to make easy the solubilization in very polar solvents. On the other hand, the interior of the cavity where only the oxygens interglycosidic are located is less polar and this zone is more hydrophobic. It is this amphiphilic character which gives to CD their more interesting property: to form supramolecular complexes in aqueous solution with an invited molecule. A number of studies were performed on the inclusion of amino benzoic acids with cyclodextrins by using circular dichroism, calorimetry, fluorimetry, NMR and UV-Vis spectroscopy methods but no theoretical study was investigated [11-19]. The experimental results obtained suggest that  $\beta$ -CD can form a stable inclusion complex with PABA than  $\alpha$ -CD. The molecular recognition interactions of PABA species by  $\alpha$ ,  $\beta$  and HP-  $\beta$ -CD were studied by using steady-state fluorescence measurement. The result shows that CDs include neutral species of PABA more than the cationic and anionic species because it is more hydrophobic [13].

Recently, Terekhova et al. [17, 18] have studied the encapsulation of PABA and MABA in  $\alpha$  and  $\beta$ -CD in aqueous solution and it was observed that PABA is more deeply included in  $\beta$ -CD than MABA. The up field shift observed in NMR spectra indicate that the aromatic ring is located between the internal hydrogens H(3) and H(5) of  $\beta$ -CD and this encapsulation is accompanied by the intensive dehydration and hydrophobic effects but no information about the orientation of ABA in  $\beta$ -CD cavity was given [18].

Since 1995, a great number of researches were focused on the study of inclusion complex of cyclodextrins by semi empirical methods AM1 and PM3 to obtain electronics properties and to have more information about geometry of the complex. The results suggested that PM3 should be more advantageous than AM1 and give results which coincide with the experimental observations [20-37]. In 2000 some studies were carried out about the performances of AM1 and PM3 methods on CD systems [26]. On the basis of AM1 and PM3 calculation results for some model compounds including  $\alpha$ -hydroxyethyl ether and  $\alpha$  (1-4)-glucobiose, it suggested that PM3 should be advantageous to AM1 in CD chemistry because PM3 can deal with the O-H...O hydrogen bonds better than AM1. This proposal was supported by direct structure optimization of  $\alpha$ - and  $\beta$ -CD with AM1 and PM3, in which AM1 gave badly distorted geometries due to unreasonable

hydrogen bonding, whereas PM3 reproduced the crystalline structures rather well.

The aim of this work is to give more information about the location of ammonium and carboxylic groups compared to position of primary or secondary hydroxyl of  $\beta$ -CD. The molecular mechanics, PM3 and AM1 methods were applied to study the formation and the geometries of inclusion complex between neutral, anionic and cationic species of PABA and  $\beta$ -CD with and without the water molecules.

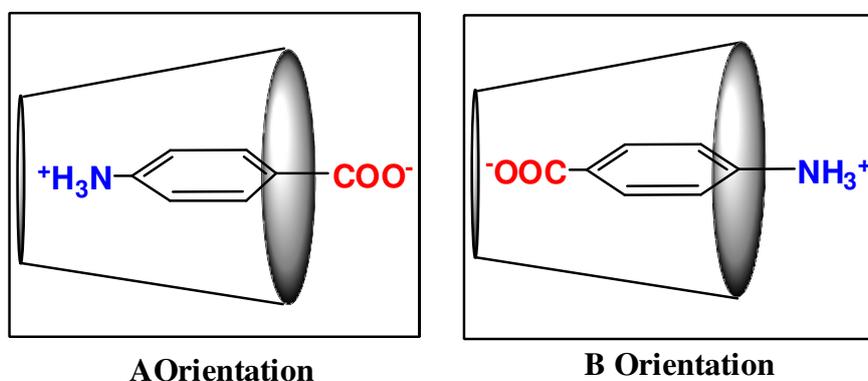
## Material and Methods

### Computational Methods

All calculations were carried out using Hyperchem 7.51 [38] and Gaussian03 software [39].

The initial structure of both species of PABA was constructed by module builder of Hyperchem then these structures were optimized by MM+ force field and both PM3 and AM1 methods (the charge +1 was set for cationic PABA, -1 for anionic specie and 0 for neutral PABA). The structure of  $\beta$ -CD was constructed by union of seven glycosidic united linked by  $\alpha$ -1,4 bend and minimized by means MM+ force field and both PM3 and AM1 methods.

To control the inclusion of PABA in  $\beta$ -CD cavity, we have studied the two possible regioselectivity (A or B). When A represent the encapsulation of the ammonium group ( $\text{NH}_2$ ) in  $\beta$ -CD cavity and the B orientation correspond to the introduction of carboxylic group ( $\text{COOH}$ ). According to the two orientations, the guest was placed in  $\beta$ -CD cavity and rotated with x, y and z axis with 10 degrees steps, then each of the systems were optimized to locate the complex with lowest energy.



**Scheme 4.** Two possible orientations of PABA in  $\beta$ -CD.

### Solvation

The lowest complex found with MM+ computation was placed in a cubic box of (20, 20, and 20) Å<sup>3</sup> which contain about 265 water molecules. The system was firstly optimized by means MM+ force field then the calculations of the single point were performed after remove of the water molecules.

The obtained structure of MM+ computations in vacuum and water solvent were reoptimized with both methods PM3 and AM1 at RMS of 0.01Kcal/mol with Polack-Ribiere algorithm and without any restriction. Finally, we note that in water we optimize the complex within including water molecules we take only the structure of the complex.

## Results and Discussion

In this study we have considered only the inclusion compounds in molar proportion 1:1 formed between one molecules of β-CD and ones of PABA species abbreviated PABA1/ β-CD (A), PABA1/ β-CD (B), PABA2/ β-CD (A), PABA2/ β-CD (B), PABA3/ β-CD (A) and PABA3/ β-CD (B) (when molecule 1, 2 and 3 represent respectively neutral, anionic and cationic species of PABA). The stabilization energy for each complex in the two orientations was calculated by both PM3 and AM1 methods, which was given by subtracting the sum of the energy of individual free host and guest molecules to the energy of the inclusion complex:

$$\Delta E = E_{\text{complex}} - E_{\beta\text{-CD}} - E_{\text{PABA}} \quad (1)$$

Table 1 resumes stabilization energy of each complex, HOMO, LUMO and the energy gap between HOMO and LUMO. The negative value of these stabilization energy showed that a stable inclusion complex was formed. The PM3 calculation realized in vacuum showed that A orientation is the most favored for the three species of PABA. Thus, the complex formed by neutral PABA prefers the encapsulation of ammonium group in β-CD cavity. This orientation is preferred by 12.17 Kcal/mol and this preference can be attributed to the formation of two H-bond: the first is a stronger H-bond which is formed between oxygen of COO<sup>-</sup> and H of secondary OH positioned at 1.77 Å, the second is formed between H of NH<sub>3</sub><sup>+</sup> and O of primary OH positioned at 3.14 Å.

PABA2/ β-CD (A) is more favored than the other complexes: In this case, three H-bonds were established: the first H-bond with a length of 2.97 Å was formed between oxygen of COO<sup>-</sup> and H of secondary hydroxyl. The second was formed between the second oxygen of COO<sup>-</sup> and H of secondary hydroxyl positioned at 1.77 Å and the third H-bond with a length of 2.74 Å was formed between O of COO<sup>-</sup> and another H of secondary hydroxyl.

**Table 1.** PM3 and AM1 stabilization energy accompanying complexation of each species of PABA in  $\beta$ -CD (Kcal/mol), interaction energy [HOMO, LUMO and their energy gap (eV)] in vacuum.

	PABA1/ $\beta$ -CD (A)	PABA1/ $\beta$ -CD (B)	PABA2/ $\beta$ -CD (A)	PABA2/ $\beta$ -CD (B)	PABA3/ $\beta$ -CD (A)	PABA3/ $\beta$ -CD (B)
PM3						
<b><math>\Delta E</math> (Kcal/mol)</b>	-124.34	-112.162	-137.40	-125.26	-97.05	-74.43
HOMO (eV)	-8.89	-8.69	-6.48	-6.08	-12.41	-12.14
LUMO (eV)	0.84	-1.58	2.43	2.65	-4.08	-4.40
$\Delta$ (HOMO-LUMO)	-9.73	-7.11	-8.92	-8.65	-8.33	-7.73
AM1						
<b><math>\Delta E</math> (Kcal/mol)</b>	-135.47	-125.67	-134.27	-126.52	-109.92	-77.352
HOMO (eV)	-9.14	-9.02	-6.28	-6.23	-12.21	-12.05
LUMO (eV)	-0.83	-1.00	2.67	2.85	-3.77	-4.08
$\Delta$ (HOMO-LUMO)	-8.31	-8.02	-8.95	-9.09	-8.44	-7.96

PABA3/  $\beta$ -CD (B) present only one H-bond between H of  $\text{NH}_3^+$  group and O of secondary hydroxyl positioned at 2.61 Å.

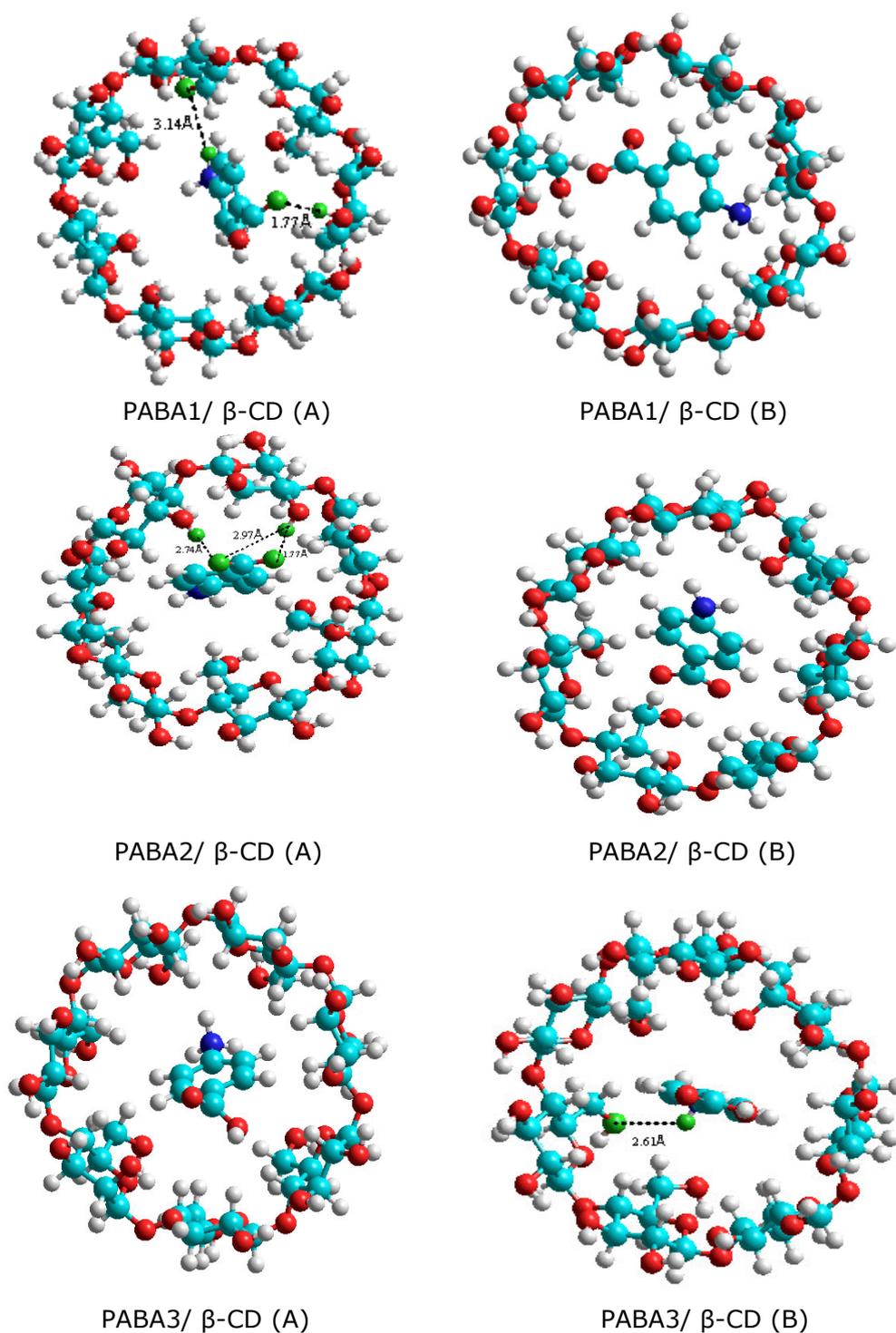
**Table 2.** PM3 and AM1 stabilization energy accompanying complexation of each species of PABA in  $\beta$ -CD (Kcal/mol) and interaction energy (HOMO, LUMO and their energy gap (eV) in water.

	PABA1/ $\beta$ -CD (A)	PABA1/ $\beta$ -CD (B)	PABA2/ $\beta$ -CD (A)	PABA2/ $\beta$ -CD (B)	PABA3/ $\beta$ -CD (A)	PABA3/ $\beta$ -CD (B)
PM3						
<b><math>\Delta E</math> (Kcal/mol)</b>	-120.52	-111.19	-138.272	-135.013	-95.810	-80.510
HOMO (eV)	-8.95	-8.63	-6.485	-7.841	-12.454	-12.113
LUMO (eV)	-1.30	-1.60	2.449	2.317	-4.068	-4.332
$\Delta$ (HOMO-LUMO)	-7.65	-7.03	-8.934	-10.158	-8.386	-7.781
AM1						
<b><math>\Delta E</math> (Kcal/mol)</b>	-135.07	-135.76	-134.956	-120.989	-109.874	-98.003
HOMO (eV)	-9.13	-9.45	-6.366	-6.281	-12.220	-11.930
LUMO (eV)	-0.82	-1.23	2.702	2.820	-3.784	-4.108
$\Delta$ (HOMO-LUMO)	-8.31	-8.22	-9.068	-9.101	-8.436	-7.822

The energy of stabilization obtained in presence of solvent was calculated after minimizing the system (water and complex), subsequently the solvent molecules were removed and a single point was performed (Table 2).

The results given in Table 2 shows that A orientation is the most favored for the three species of PABA. Thus, for the neutral PABA, A orientation is favored by 9.33 kcal/mol with respect to B and in this case two H-bond were established, the first between O of  $\text{COO}^-$  and H of secondary OH positioned at 1.78 Å and the second between

H of  $\text{NH}_3^+$  and O of primary OH positioned at 3.15 Å.



**Scheme 5.** Structures of the energy minimum obtained by the PM3 calculations in vacuum (with Hyperchem).

However in the B orientation PABA1/  $\beta$ -CD complex only one H-bond was observed between H of  $\text{NH}_3^+$  and O of secondary OH positioned at 2.76 Å.

For the charged complexes the preference of A orientation is of 3.25 kcal/mol for anionic complex and 15.30 kcal/mol for cationic complex.

Regarding the PABA2/  $\beta$ -CD (A) complex has two H-bonds: the first was established between O of ( $\text{COO}^-$ ) and H of secondary hydroxyl at distance of 1.77 Å, the second was formed between O of ( $\text{COO}^-$ ) and other H of a secondary hydroxyl positioned at of 1.75 Å which is in good agreement with experimental results [19].

By the same manner we observed for PABA3/  $\beta$ -CD complex in A orientation one H-bond was formed between H of  $\text{NH}_3^+$  and O of a primary hydroxyl at 2.53 Å.

The energies of HOMO and LUMO of the complexes are summarized in Tables 2 and 3. From these tables, it can be seen that the elevation of HOMO and depression of LUMO energy causes more change in electronic properties.

The geometries of the studied complexes found by PM3 methods showed that PABA species were deeply included in  $\beta$ -CD especially for A orientation.

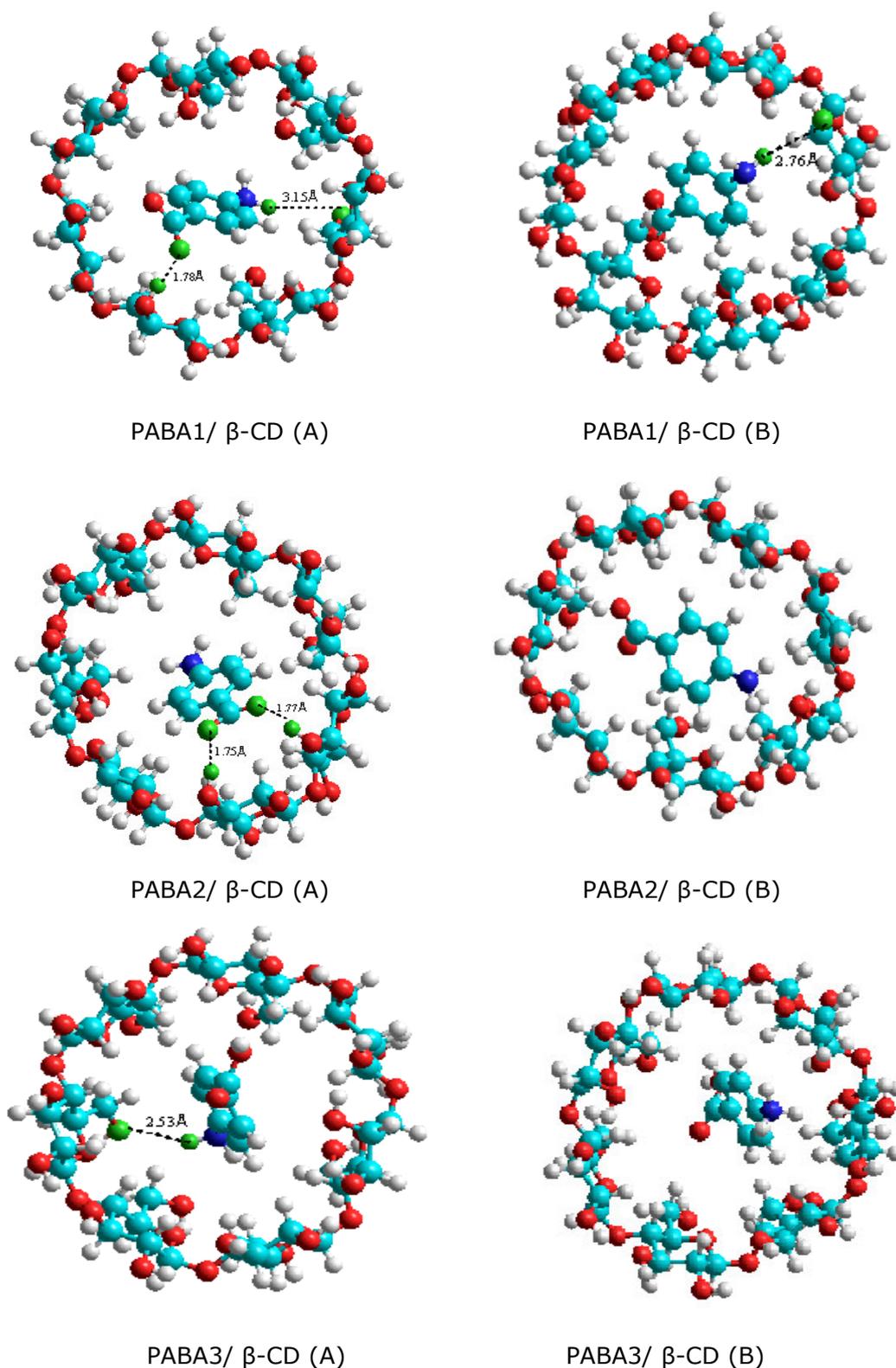
The results presented in Table 3 obtained by DFT single point calculations showed that the stabilization energy of the complexes are negative, attest that these complexes are stable.

For the neutral PABA A orientation is favored by 10.50 Kcal/mol with respect to the B orientation. In the case of cationic PABA the preference of A orientation is of 17.95 Kcal/mol, for the anionic PABA the energetic gap is of 0.13 Kcal/mol which suggest that the two orientations coexist.

In presence of water molecules A orientation is favored by 26.46 Kcal/mol and 30.78 Kcal/mol for anionic and cationic complexes respectively.

**Table 3.** B3LYP/6-31G stabilization energy accompanying complexation of each species of PABA in  $\beta$ -CD (Kcal/mol).

	PABA1/ $\beta$ -CD (A)	PABA1/ $\beta$ -CD (B)	PABA2/ $\beta$ -CD (A)	PABA2/ $\beta$ -CD (B)	PABA3/ $\beta$ -CD (A)	PABA3/ $\beta$ -CD (B)
	In vacuum					
$\Delta E$ (Kcal/mol)	-83.70	-73.20	-82.96	-83.09	-45.11	-27.16
	In water					
$\Delta E$ (Kcal/mol)	-80.04	-80.78	-96.05	-69.59	-50.16	-19.38



**Scheme 6.** Structures of the energy minimum obtained by the PM3 calculations in water (with Hyperchem).

## Conclusion

The calculations carried out by PM3 and AM1 methods shows that inclusion complex of the PABA species in  $\beta$ -CD are stables and this confirm experimental observations. During this theoretical study A orientation was found more favorable than B orientation. We note that the aromatic ring for each species of PABA is totally embedded in  $\beta$ -CD cavity, the COO group is faced to secondary hydroxyls of  $\beta$ -CD and the NH<sub>2</sub> group is faced to primary hydroxyl. This preference can be attributed to the establishment of a great number of H-bond in A orientation. Finally, we can say that the geometries of the complexes do not change in presence of water molecules and the energetic gap between A and B orientation for each species in water is less than that in vacuum, we can note that PM3 explain better  $\beta$ -CD/PABA system.

## Acknowledgements

This study was supported by Algerian Minister of Scientific Research (research project 01/01/2005).

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