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Molecular modeling study of para-amino benzoic acids recognition by β-cyclodextrin

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ABSTRACT

AM1 and PM3 methods were applied to investigate equilibrium geometries of inclusion complexes formed between β-CD and neutral, anionic and cationic species of PABA (Para-amino benzoic acid). B-CD can bind this three species (two possible orientations A or B) with negative binding energy, were 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 complexes were calculated and compared.

Key words*:* PABA, Cyclodextrin, inclusion complex, PM3, AM1, B3LYP/6-31G.

INTRODUCTION

Para-aminobenzoic acid (PABA) is an isomeric form of amino benzoic acid (ABA) of that is often thought of 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 used to improve the protein used in the body, 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) as the pH of the environment. PABA application is limited because it posses a lower fluorescence emission and it can damage DNA after UV irradiation. To avoid these effects PABA was used as a complexed form in CDs. This inclusion can increase aqueous solubility and fluorescence emission.

Cyclodextrins (CDs) are well-known sugar oligomer built up from glucopyanose units. Each unit is bonded to the other through *a*-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. 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.

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

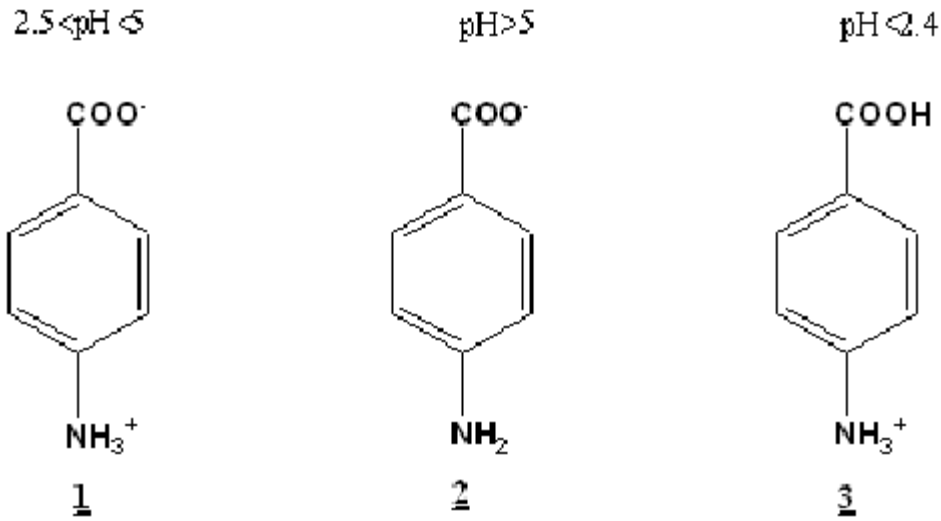
A number of studies were performed on the inclusion of amino benzoic acids with cyclodextrins by using circular dichroism, calorimetry, fluorimetry, NMR and UV-Vis spectroscopy methods[11-19], the results suggest that

β-CD can form a stable inclusion complex with PABA than α-CD, but no theoretical study was investigated. The molecular recognition interactions of PABA species by α, β and HP- β-CD were studied by using steady-state fluorescence measurement, the results shows that CDs include neutral specie of PABA more than the cationic and anionic species because it is more hydrophobic[13].

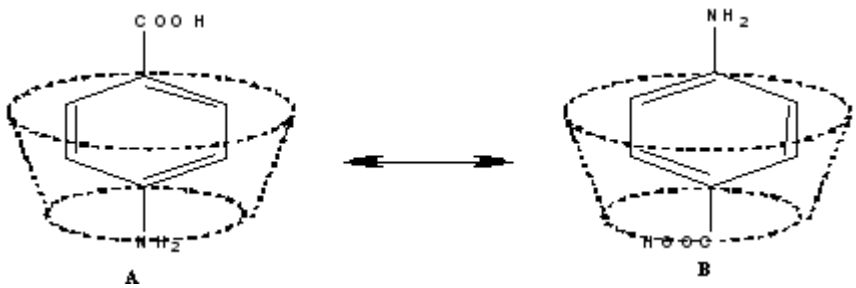
Recently, Irina V and al have studied the encapsulation of PABA and MABA in α and β-CD in aqueous solution it observed that PABA is deeply included in β-CD than MABA and the aromatic ring of ABA is located between the internals hydrogen's H (3) and H (5) of β-CD because it provided their up field shift and this encapsulation is accompanied by the intensive dehydratation and hydrophobic effects but no information about the orientation of ABA in β-CD cavity[18].

Since 1995, a great number of researches was focused on the study of inclusion complex of cyclodextrins by semi empirical methods AM1 and PM3 to obtain electronics properties and gives more information about geometry of the complex. The results suggested that PM3 should be more advantageous than AM1 and give results approached to experimental observations[20-37].

The aim of this work is to information about the location of ammonium and carboxylic groups toward primary or secondary hydroxyl of β-CD. The



Scheme 1: species form of PABA at different pH values



Scheme 2: Two possible orientations of PABA in β-CD

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 β-CD in presence and in absence of water solvent.

Computational methods

All calculations were performed in Hyperchem 7.51 [38], and Gaussian03 software[39].

The initial structure of both species of PABA was constructed by module builder of Hyperchem, and then these structures were optimized by MM+ and both methods PM3 and AM1 methods. The structure of β-CD was constructed by union of seven glycosidic united linked by α-1,4 bend and minimized by means MM+ force field and both PM3 and AM1 methods.

To control the inclusion of PABA in β-CD cavity, we have studied the two possible regioselectivity (A or B). When A represent the encapsulation of the ammonium group (NH_2) in β-CD cavity and the B orientation correspond to the introduction of carboxylic group (COOH). According to the two orientations, the guest was placed in â-CD cavity and rotated with x, y and z axis with 10° steps in each the system was optimized to locate the complex with lowest energy.

Salvation

The lowest complex found with MM+ computation was placed in a cubic box of (20, 20, and 20) $Å^3$ which contain about 265 water molecules. The system was optimised by means MM+ force field. Then the solvent molecules were removed and a single point was performed.

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 writhing any restriction. In water we optimize the complex within including water molecules we take only the structure of the complex.

RESULTS AND DISCUSSION

In the following 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 molecule1, 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.

$$\Delta E = E_{complex} - E_{\beta-CD} - E_{PABA}$$

Table 1: PM3 and AM1 stabilization energy accompanying complexation of each species of PABA in β-CD (KCal/mol) , interaction energy (HOMO, LUMO and their energy gap (eV)) in vacuum

	PABA1/ β-CD (A)	PABA1/ β-CD (B)	PABA2/ β-CD (A)	PABA2/ β-CD (B)	PABA3/ β-CD (A)	PABA3/ β-CD (B)
			PM3			
ΔE(Kcal/mol)	-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
Δ(HOMO-LUMO)	-9.73	-7.11	-8.92	-8.65	-8.33	-7.73
			AM1			
Δ E (Kcal/mol)	-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
Δ(HOMO-LUMO)	-8.31	-8.02	-8.95	-9.09	-8.44	-7.96

Table 1, resume 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. The complex formed by neutral PABA prefers the encapsulation of ammonium group in β-CD cavity; these orientation is preferred by 12.17 Kcal/mol when two H-bond were formed: the first is a stronger H-bond which is formed between oxygen of COO^- and H of secondary OH at a distance of 1.77Å, the second is formed between H of NH_3^+ and O of primary OH at a distance of 3.14 Å.

PABA2/ β-CD (A) is more favored than the other complexes: three H-bonds were established: the first distant of 2.97Å was formed between oxygen of COO^- and H of secondary hydroxyl, the second was formed between oxygen of $COO^-$and H of secondary hydroxyl at a distance of 1.77 Å, the third H-bond distant of 2.74 Å was formed between O of COO^- and an other H of secondary hydroxyl. PABA3/ β-CD (B) present H-bond between H of NH^+_3 group and O of secondary hydroxyl at 2.61 Å.

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

A orientation is the most favored for the

Table 2: PM3 and AM1 stabilization energy accompanying complexation of each species of PABA in β-CD (KCal/mol) and interaction energy (HOMO, LUMO and their energy gap (eV)) in water

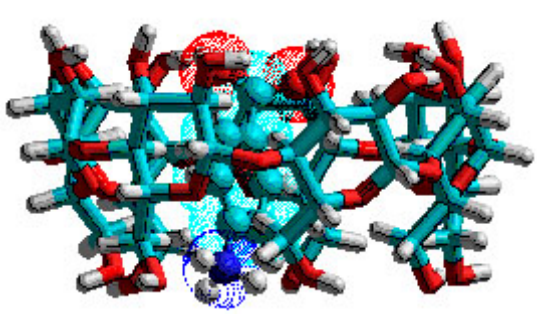
	PABA1/ β-CD (A)	PABA1/ β-CD (B)	PABA2/ β-CD (A)	PABA2/ β-CD (B)	PABA3/ β-CD (A)	PABA3/ β-CD (B)
			PM3			
ΔE(Kcal/mol)	-120.52	-111.19	-138.272	-135.013	-95.810	-80.510
HOMO (eV)	-8.95	-8.63	-6.485	-7.841	-12.454	-12.113
LUMO (eV)	-1.30	-1.60	2.449	2.317	-4.068	-4.332
Δ(HOMO-LUMO)	-7.65	-7.03	-8.934	-10.158	-8.386	-7.781
			AM1			
Δ E (Kcal/mol)	-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
Δ (HOMO-LUMO)	-8.31	-8.22	-9.068	-9.101	-8.436	-7.822

Table 3: B3LYP/6-31G stabilization energy accompanying complexation of each species of PABA in β-CD (KCal/mol)

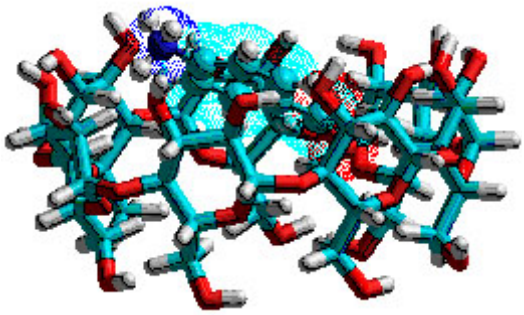
	PABA1/ β-CD (A)	PABA1/ β-CD (B)	PABA2/ β-CD (A)	PABA2/ β-CD (B)	PABA3/ β-CD (A)	PABA3/ β-CD (B)
			In vacuum			
ΔE(Kcal/mol)	-83.70	-73.20	-82.96	-83.09	-45.11	-27.16
			In water			
Δ E (Kcal/mol)	-80.04	-80.78	-96.05	-69.59	-50.16	-19.38

three species of PABA; for the neutral PABA, A orientation is favored by 9.33kcal/mol with respective to B; two H-bond were established, the first was formed between O of COO^- and H of secondary OH at a distance of 1.78 Å, the second was formed between H of NH_3^+ and O of primary OH at a distance of 3.15 Å.

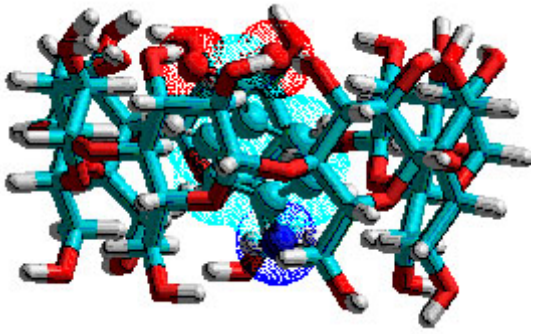
PABA1/ β-CD (B) complex present H-bond between H of NH_3^+ and O of secondary OH at a distance of 2.76 Å.



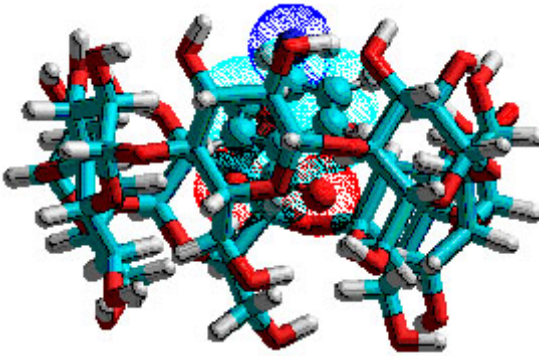
PABA1/ β-CD (A)



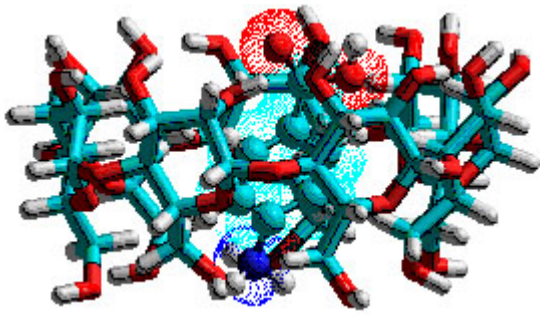
PABA1/ β-CD (B)



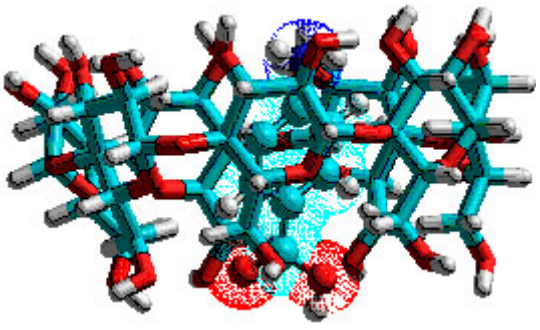
PABA2/ β-CD (A)



PABA2/ β-CD (B)



PABA3/ β-CD (A)

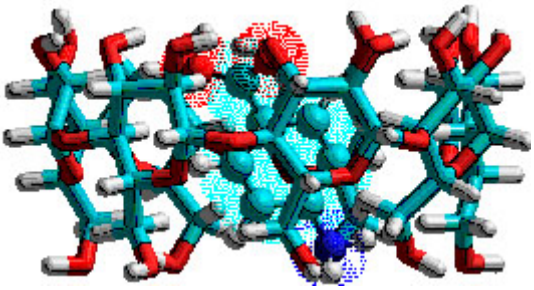


PABA3/ β-CD (B)

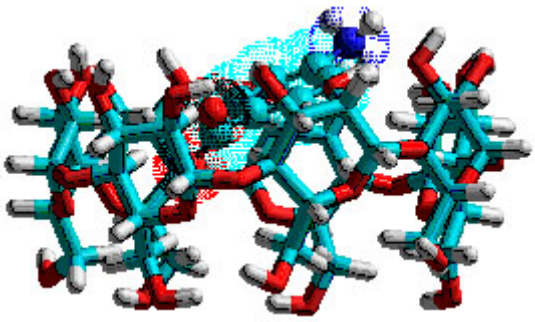
Fig. 1: structures of the energy minimum obtained by the PM3 calculations in vacuum

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

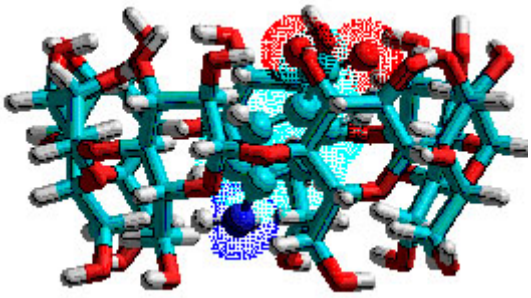
For PABA3/ β-CD (A) an H-bond was formed between H of NH_3+ and O of a primary hydroxyl at 2.53Å



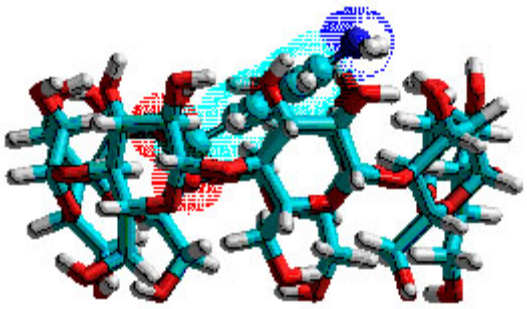
PABA1/ β-CD (A)



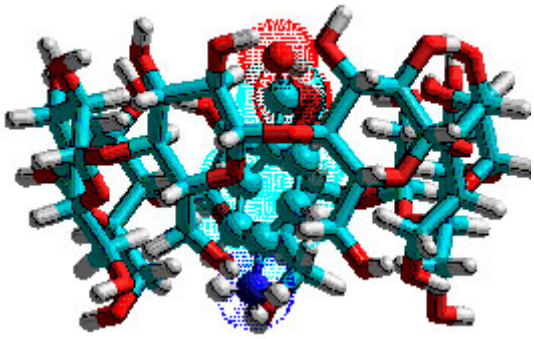
PABA1/ β-CD (B)



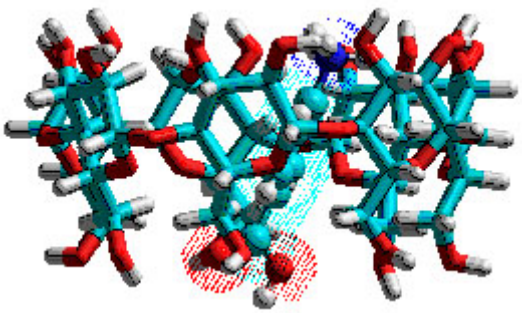
PABA2/ β-CD (A)



PABA2/ β-CD (B)



PABA3/ β-CD (A)



PABA3/ β-CD (B)

Fig. 2: Structures of the energy minimum obtained by the PM3 calculations in water

Based on the above results, AM1 give the same results as of PM3 calculation, but for the neutral complex in presence of water solvent B orientation is favored by 0.69kcal/mol with respect to A orientation.

It was the H-bond interaction between the β-CD and PABA species that changed the electronic properties to a certain level, most important to the elevation of HOMO energy and depression of LUMO energy in the studied complexes.

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

The results presented in table 3 showed that the stabilization energy of the complexes are negative and shows that A orientation is the most stable conformation in vacuum and in water.

CONCLUSION

The calculations carried out by PM3 and AM1 methods shows that inclusion complex of the PABA species in β-CD are stables and confirm experimental observations. During this theoretical study A orientation is the most favored when aromatic ring for each species of PABA is totally embedded in β-CD cavity, COO group is faced to secondary hydroxyls of β-CD and NH2 group is faced to primary hydroxyl. This preference is due to the establishment of a great number of H-bond in A orientation. These observations are similar in presence or in absence of water molecules.

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