J Incl Phenom Macrocycl Chem (2012) 73:305–312
DOI 10.1007/s10847-011-0057-9

ORIGINAL ARTICLE

Computational studies of 1:2 complex between retinol propionate and β cyclodextrin

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Received: 4 June 2011 / Accepted: 25 September 2011 / Published online: 6 November 2011

Abstract [M05-2X/6-31G*:PM3MM] and [B3LYP/6-31G*:PM3] ONIOM2 methods have been used to investigate the vitamin A propionate/β cyclodextrin complex with 1:2 stoichiometry. Both methods give almost the same lowest energy minimum. The minimum energy structure of the complex is found in good agreement with experimental data. In this configuration, the major structure of propionate of vitamin A (PVA) is embedded inside the two cavities of βCD while the propionate group is kept outside. However, the three methyl groups of PVA are positioned in the free space between both βCD molecules. The driving forces for complexation are dominated by Van der Waals interactions between PVA and the βCD molecules assisted with multiple hydrogen bond interactions between the two cyclodextrin molecules. These interactions were investigated using the natural bond orbital approach.

Keywords Inclusion complexes · PVA · Cyclodextrin · PM3 · Host–guest interactions · ONIOM · NBO

Introduction

'Vitamin A' refers to a group of polyunsaturated hydrocarbons with important nutritional roles in humans, the main compounds in this group are the retinoids, which are chemical derivatives of retinol, and provitamin A carotenoids [1].

In the therapeutic field, the efficiency of a drug depends in part on its physical properties, among these, two should be very good, aqueous solubility and chemical stability, when a molecule does not fit these criteria, its use becomes more complicated what leads to reduce its applications. Pure vitamin A, which corresponds to retinol, is too unstable to allow for routine use in laboratory scale, thus, it is much more common to use one of its esters, whose activity is near [2].

Propionate of vitamin A (PVA) (Fig. 1-b) was chosen among several esters of vitamin A on the basis of a preliminary study of its inclusion into CDs. PVA is a highly unstable and poorly water soluble molecule which has a real interest in therapeutic.

Cyclodextrins are natural cyclic oligosaccharides that were discovered >100 years ago [3], they have a hydrophilic outer surface and a lipophilic central cavity. They consist of (α-1, 4-)-linked α-D-glucopyranose units with a lipophilic central cavity. Due to the chair formation of the glucopyranose units, cyclodextrin molecules are shaped like cones with secondary hydroxy groups extending from the wider edge and the primary groups from the narrow edge (Fig. 1-a). This gives cyclodextrin molecules a hydrophilic outer surface, whereas the lipophilicity of their central cavity is comparable to an aqueous ethanolic solution [4]. This allows the formation of the inclusion complex by admitting inside the cavity one or more invited molecules without to establish of covalent bond [5]. The most common natural cyclodextrins consist of six (α-cyclodextrin), seven (β-cyclodextrin) and eight (γ-cyclodextrin) glucopyranose units. Although the natural cyclodextrins and their complexes are hydrophilic, their

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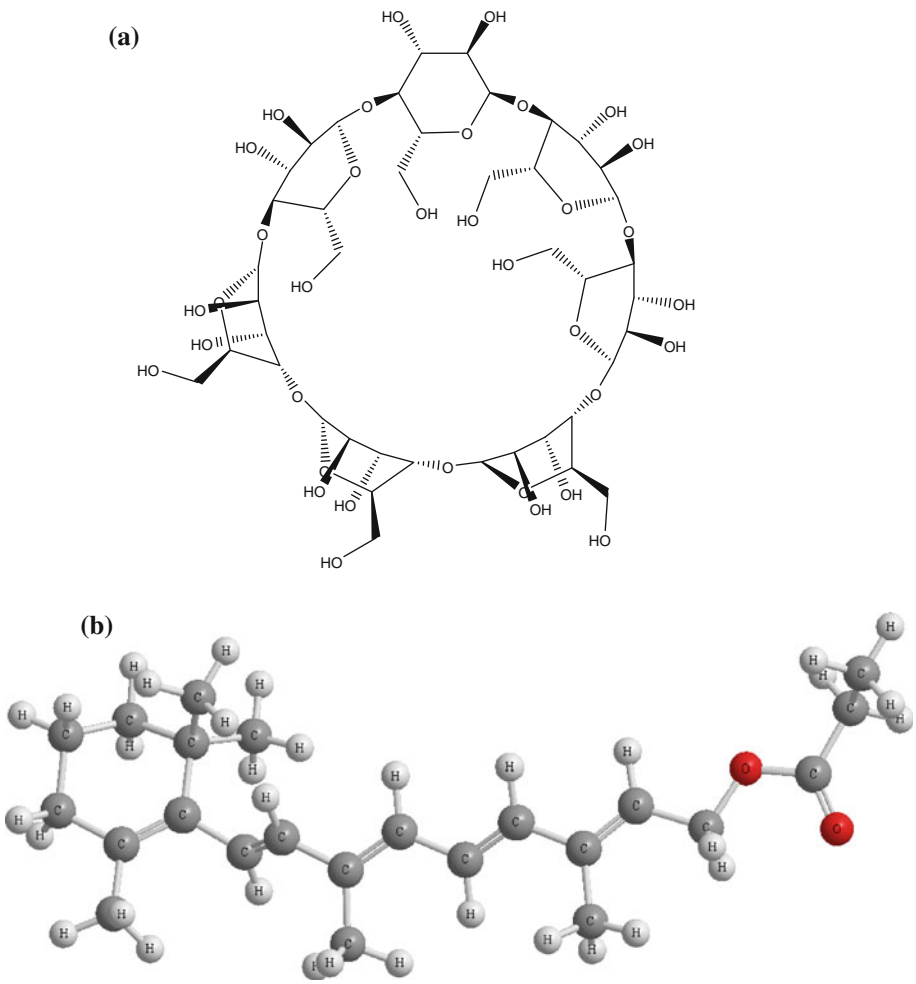


Fig. 1 **a** The scratch of βCD. **b** Structure of PVA ($C_{23}H_{34}O_2$)

aqueous solubility is rather limited, especially that of β-cyclodextrin [6].

The stoichiometry of complexation is verified through Job's plots or nuclear magnetic resonance (NMR) studies, but these are typically performed in dilute solutions in contrast with phase-solubility studies which are based on investigations of saturated drug solutions. Theoretical computer modelling can also be used to assess steric interaction of complexation and have been used to predict the nature of drug–cyclodextrin interaction in either vacuum or ideal solutions [7].

Integration of the signals of the $_1$H-NMR spectrum in D6-DMSO of PVA/βCD complex allowed determining easily and without any doubt the PVA/βCD ratio in the complex, the results are: 1:2 complex for PVA/βCD [2]. This 1:2 stoichiometry has already been reported for other vitamin A esters such as palmitate and acetate [8, 9].

These results are in adequacy with the size of the cavities of the CDs: since the βCD is smaller it is possible that the part of the PVA molecule that remains outside the cavity can be included in a second βCD molecule [2].

In this paper we study theoretically the stability of PVA/βCD complex with stoichiometry 1:2 starting from simple 1:1 associations, using PM3 semi-empirical method and hybrid method (ONIOM2) with the aim to determine its geometry and conformational changes of PVA inside the βCD cavity.

In order to find more accurate results we optimize the system with M05-2X:PM3MM. We used this later functional which is proposed by Zhao and Thruhla's [21] because it is well suited for non bonded interactions and leads to results which as reliable as B3LYP's regarding the ground state properties. This functional was assisted with PM3 with MM corrections.

Finally the natural bond orbital analyses (NBO) were applied as a powerful approach for the evaluation of the intermolecular interactions between the three molecules.

Computational method

The calculations were carried out using MOPAC2009 [10], and the Gaussian 03 quantum mechanical package [11].

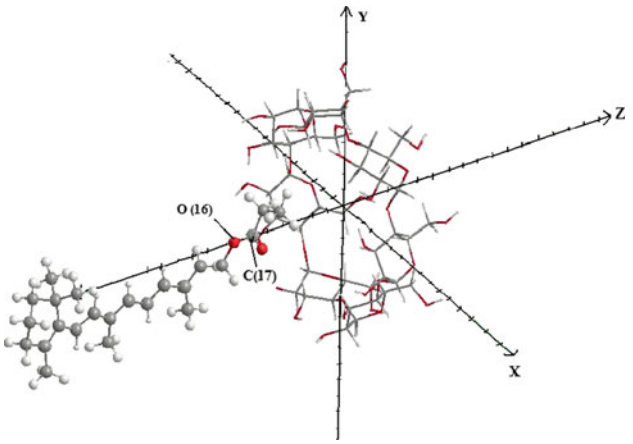


Fig. 2 Position of PVA in front of β-CD before complexation with using bond O(16)–C(17) as reference bond

The initial structure of PVA is constructed with the help of Hyperchem (release 6.0, Hypercube, Inc) using Amber force field. βCD was taken with its optimization form from Chem-office 3D ultra (version 6.0, Cambridge software).

We start the construction of 1:1 stoichiometry complex of PVA/βCD such as the glycosidic oxygen atom of βCD were placed onto the *XY* plane, the center of βCD was defined as the origin of the coordinate system narrow rim at a distance of 6 Å which separates the βCD equatorial plane and the reference bond C(17)–O(16) of the guest molecule which is placed on the *Z* axis and was allowed to approach the βCD cavity from the reference bond (Fig. 2).

The inclusion process is then achieved along the *Z* axis until the molecule exit the cavity at $\sim$22 Å with a step of 1 Å. At every step of translation, the PVA was rotated around the *Z* axis at 20° intervals from 0 to 360°.

Taking the host molecule completely restricted, the generated structures at each step were successively optimized with MM2 and PM3 methods. (Fig. 3).

Secondly, starting the energy minimum structure of the PVA:βCD (1:1) complex obtained in the first step, a second βCD molecule was placed on the origin facing the complex in which we have the secondary hydroxyl side of the two CD is facing each other and will be connected by hydrogen bonds to create barel-like cavity (Fig. 4). The arrangement head–head CD dimer was chosen because it was found more stable in numerous studies.

Then, the full PVA:βCD (1:1) complex was moved by step along the *Z*-axis by referring to the C3 atom, from 1 to 12 Å by 1 Å. At each step the system was optimized with PM3.

Finally, once the PVA-βCD (1:2) complex was obtained and in order to explore the maximum space inside the cavity βCD dimer for finding an even more stable structure, the PVA molecule was translated and rotated inside the cavity on a distance around 6 Å. At each position the

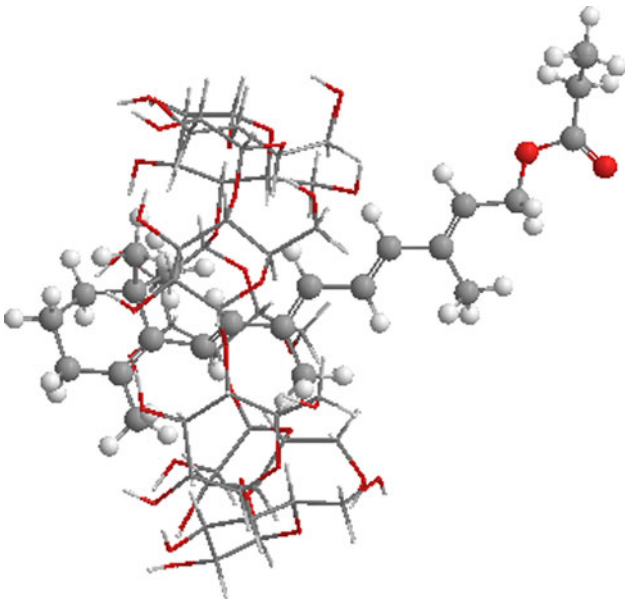


Fig. 3 Geometrical structure of complex1:1 after complexation and optimization at PM3

system was optimized firstly with PM3 and ONIOM2 [RB3LYP/6-31G*:PM3] methods. In order to find more accurate results in ONIOM method the high level M05-2X/6-31G* was carried out on PVA and the low level PM3MM on βCD.

The energy minima was determined in terms of complexation energy ($E_{complexation}$) who was estimated for both complexes according to the relations:

$$E_{complexation} = E_{complex1:1} - \left(E_{opt\beta CD} + E_{optPVA}\right) \quad (1)$$

$$E_{complexation} = E_{complex1:2} - \left(2E_{opt\beta CD} + E_{optPVA}\right) \quad (2)$$

Where $E_{complex\ 1:1}$, $E_{opt\ \beta CD}$, $E_{opt\ PVA}$ in Eq. 1 denote, respectively, the total energy of the 1:1 complex, the free host molecule (βCD) and the free guest molecule (PVA). In Eq. 2 $E_{complex\ 1:2}$ denotes the energy of 1:2 complex and the others are as above [12]. The magnitude of the energy change would be an indicator of the driving forces towards complexation.

The deformation energy for each component, host and guest throughout the formation of the complex was defined as the difference in the energy of the totally optimized component compared to its energy in the complex [13].

$$DEF(component) = E(component)_{sp}^{opt} - E(component)_{opt} \quad (3)$$

The ONIOM method which means "Our own N-layer Integrated molecular Orbital and molecular Mechanics" is a hybrid computational method that allows different levels of theory to be applied to different parts of a molecular system. Thus, in the two-layered ONIOM method, the molecular system under-study is divided into an inner and

outer layer, the inner layer consists of the most critical elements of the system, and the rest of the system comprises the outer layer [14].

In the terminology of Morokuma and co-workers [15, 16] the full system is called "real" and is treated with a low level of theory. The inner layer is termed "model" and is treated with both the low and the high level of theory. The total ONIOM energy E^{ONIOM} is then given by the equation below:

$$E^{ONIOM} = E(high, model) + E(low, real) - E(low, model) \quad (4)$$

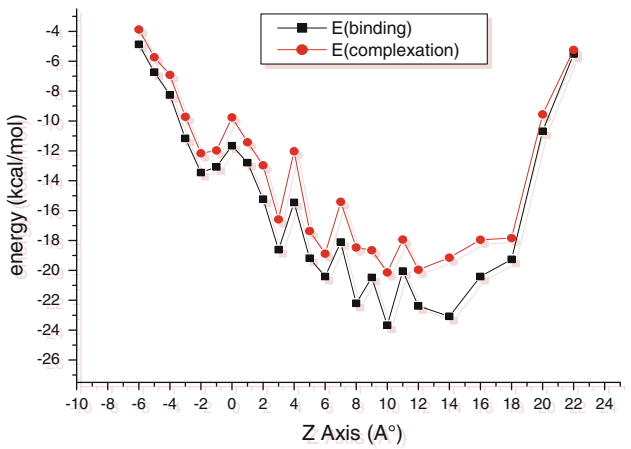
Where E (high, model) is the energy of the inner layer (PVA) at the high level of theory, E (low, real) is the energy of the entire system at the low level of theory (the complex), and E (low, model) is the energy of the model system (outer layer: 2β-CD) at the low level of theory.

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 B3LYP/6-31G(d) and M05-2X/6-31G(d) methods in order to understand various second-order interactions between the filled orbitals of one subsystem and vacant orbitals of another subsystem, which is a measure of the intermolecular delocalization or hyper conjugation.

Results and discussion

Complexation

We have started our complexation from stoichiometry 1:1 (Fig. 2) using for optimization the semi-empirical method PM3 which is highly computational efficiency for the inclusion complexes [5].



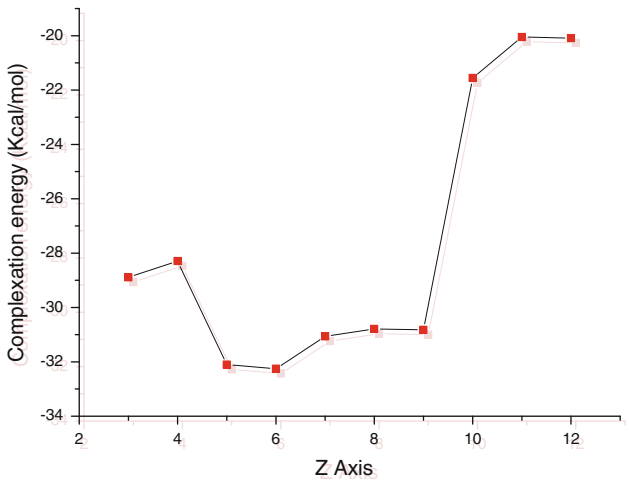
Scheme 1 Binding and complexation energies of complex PVA/βCD 1:1 at different positions

The graphical representation of the energy changes (complexation of both complexes, and binding only in the case of 1:1 complex) involved during the inclusion passing process of PVA in βCD at different position Z are illustrated in Schemes 1, 2. The obtained results indicate that energy of complexation is in agreement with energy binding in the case of complex 1:1.

For complex 1:2 we have only calculate complexation energy.

The results summarized in (Table 1); (scheme 1) show that the most stable complex 1:1 is around 10 Å between C (17)–O (16) reference bond and the origin of *Z* axis with energy of complexation equal–20.14 kcal/mol. And for complex 1:2 the complexation energy of most stable complex is about −32.25 kcal/mol with a distance of 6 Å between the reference carbon C(3) in complex 1:1 and the second βCD. The deformation of PVA in complex 1:1 is 1.41 kcal/mol and in case of complex 1:2 is 1.68 kcal/mol. Also, all the energetic values upon complexation process are negative which means that the PVA/βCD complex is thermodynamically stable.

Despite the small energy difference between the two complexes corresponding at distance 5 and 6 Å between reference atom (C3) and origin of *Z*-axis, we take as most



Scheme 2 Complexation energy of complex PVA/βCD 1:2 at different positions (Z)

Table 1 Heats of formation, Ebinding, Ecomplexation, and DEF of PVA for complex 1:1 and 1:2

Energy (Kcal/mol)	Complex 1:1	Complex 1:2
ΔH_f	−1550.19	−3020.59
$E_{binding}$	−23.66	−38.04
$E_{complexation}$	−20.14	−32.25
DEF (PVA)	1.41	1.68

optimized complex which is at 6 Å, since we will process the movement of the PVA into both cavities of βCDs.

Optimization of PVA into cavities of the two βCD

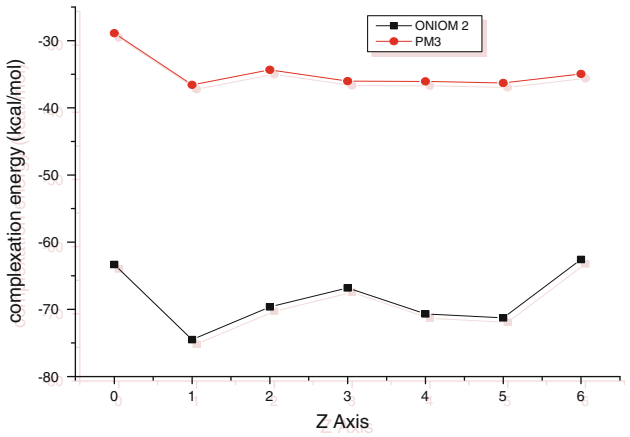
In order to refine our results, we proceed to the translation and the rotation of the PVA into both cavities of the two βCD whose are totally restricted. The methods used of optimization of complex 1:2 at every step are first PM3. As shown in (scheme 3); (Table 2), we can notice that the lowest energy of complexation is about −36.57 kcal/mol, and located around 1 Å.

But PM3 calculations present a slight decrease in the complexation energy of the whole system, therefore we adopted ONIOM2 method (RB3LYP 6-31G*/RPM3) in order to further precision of our results and for understand molecular recognition between the host and the guest, such a way that the system was divided into two part; the most important part consisting of the guest molecule (PVA) for the inner layer, and the minor part, consisting of the remaining part (2 βCDs) for the outer layer.

We remark that the curves of the complexation energies obtained with PM3 and ONIOM2 present almost the same profile (scheme 3), and the most stable complex is located around 1 Å with a complexation energy equal −74.61 kcal/mol.

In order to investigate more accurately complexation energies, hydrogen bonding and van der Waals interactions we made apply M05-2X/6-31G(d) level to PVA and PM3MM level to cyclodextrins molecules. The geometry optimisation led us to almost the same optimized structure as that obtained at B3LYP/6-31G(d):PM3 level. The results are given in Table 3. The binding energy being equal to −31.14 kcal/mol (versus −30.75 kcal/mol when using M05-2X:PM3MM level).

In Fig. 5 is exhibited the energy minimum structure obtained with ONIOM 2 [M05-2X/6-3G(d):PM3MM] method. As we can see, the cavity accommodates a moiety of cyclohexen of the PVA molecule in such way to keep the three methyl group of PVA, H_3C_{19}, H_3C_{20} and H_3C_{21} in the barel-like cavity between the two cyclodextrin molecules. However, the hydrocarbon chain of PVA molecule is linearly aligned with the channel cavity. As the size of the PVA molecule is more than the depth of the βCD cavity the polar group is kept at the hydrophilic exterior outside the cavity without establishing any interaction with the CD molecules.



Scheme 3 Energy of complexation and energy ONIOM of complex PVA/βCD 1:2 at different Z

Table 2 Heats of formation, ONIOM energy, complexation and deformation energies with PM3 and ONIOM methods of complex 1:2

Energy (Kcal/mol)	PM3	Energy	B3LYP/6-31G*
ΔHf	−3025.28	E^{ONIOM}	−660173.87
$E_{complexation}$	−36.578	$E_{complexation}$	−74.51
DEF (PVA)	0.66	DEF (PVA)	0.032

Hydrogen bonding and population analysis

NBO analysis provides an efficient method for studying intra and intermolecular bonding and interaction among bonds, and also provides a convenient basis for investigating charge transfer or conjugative interaction in molecular systems. Some electron donor orbital, acceptor orbital and the interacting stabilization energy resulted from the second-order micro-disturbance theory are reported [17, 18]. The second-order Fock matrix was carried out to evaluate the donor–acceptor interactions in the NBO analysis [19]. The interactions result is a loss of occupancy from the localized NBO of the idealized Lewis structure into an empty non-Lewis orbital. For each donor (i) and acceptor (j), the stabilization energy E (2) associated with the delocalization i → j is estimated as:

Table 3 Binding energies of the PVA:βCD complex (1:2)

Method	Complex (u.a)	PVA (u.a)	Two CD (u.a)	Binding energy (kcal/mol)
B3LYP 6-31G(d):PM3	−1052.0541714	−1047.33827572	−4.66626065	−31.14
M05-2 × 6-31G(d): PM3MM	−1051.90420749	−1047.18895279	−4.66624635	−30.75

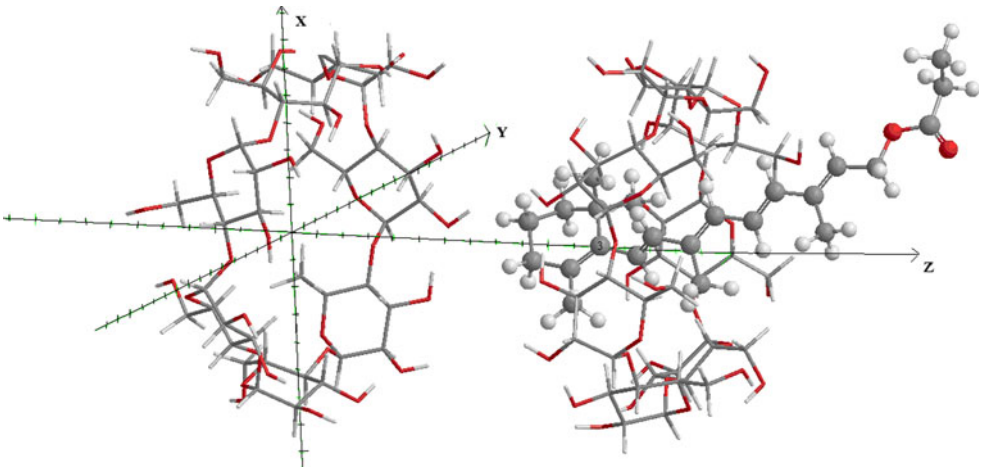


Fig. 4 Position of complex 1:1 in front of the second β-CD before complexation with using atom C(3) as reference atom

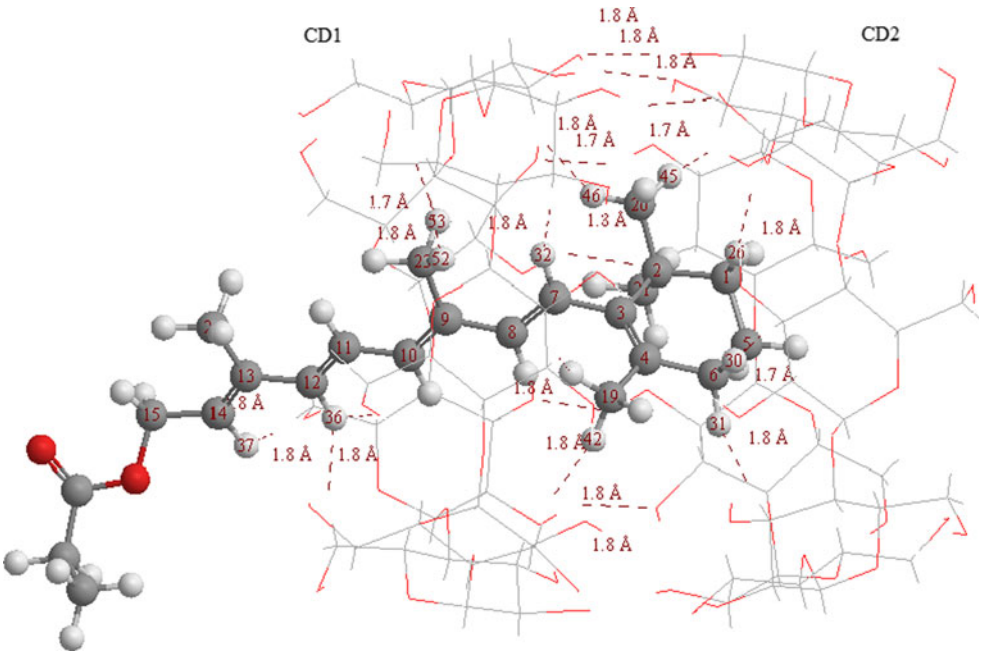


Fig. 5 Structure of the lowest energy minima of the PVA:βCD (1:2) complex

$$E(2) = \Delta E_{ij} = \frac{q_i F(i,j)}{\varepsilon j - \varepsilon i}$$

Where q_i is the donor orbital occupancy, εi and εj are diagonal elements and $F(i, j)$ is the off diagonal NBO Fock matrix element [20].

According the results obtained from NBO calculations we can conclude that the mainly forces driving during the process of formation of the inclusion complex are: hydrogen bonding between the CD molecules and van der Waals interactions between PVA molecule and atoms of cyclodextrines.

(a) Hydrogen bonding

The values of $E^{(2)}$ energies stabilization of hydrogen bonding of the PVA: βCD complex are reported in Table 4. Short-range interactions observed in the PVA: βCD complex are illustrated in Fig. 5. H-bonds (between two CD molecules) and van der Waals (between PVA and CD molecules) are shown with dashed dark lines.

NBO analysis of the structure showed that there is no hydrogen bonding interactions between PVA and CD molecules and it is only established between the two CD molecules. Thus, as it can be seen the interaction energies vary to 1–2.5 kcal/mol; these values are typically common hydrogen bond for which the energies vary between 1 and 5 kcal/mol. We remark also that the difference in hydrogen bonding calculated with both B3LYP/6.31G(d) and M05-2X/6-31G(d) methods is very small and not exceed 0.22 kcal/mol.

The hydrogen bond is defined here as an O–H…O interaction in which the H···O distance is less or equal to 3.0 Å and the O···H···O angle is greater than 145°.

Table 4 $E^{(2)}$ hydrogen bonds interactions energies in Kcal/mol

CD1 proton acceptor and CD2 donor		B3LYP/6.31G(d)	M05-2 × 6.31G(d)	Δ
LP (O 103)	σ* O279–H351	2.28	2.50	0.22
LP (O 108)	σ* O274–H348	1.79	1.98	0.19
LP (O 113)	σ* O269–H345	1.85	2.08	0.23
LP (O 118)	σ* O264–H342	1.66	1.65	0.01
LP (O 123)	σ* O259–H339	1.55	1.51	0.04
LP (O 128)	σ* O254–H339	1.57	1.52	0.05
LP (O 133)	σ* O245–H333	1.74	1.69	0.05
CD2 proton acceptor and CD1 donor				
LP (O 250)	σ* O132–H204	1.40	1.35	0.05
LP (O 255)	σ* O127–H201	1.63	1.60	0.03
LP (O 260)	σ* O177–H195	1.57	1.51	0.06
LP (O 265)	σ* O264–H342	1.67	1.62	0.05
LP (O 270)	σ* O112–H192	1.51	1.45	0.06
LP (O 280)	σ* O102–H186	1.06	1.18	0.12

Table 5 $E^{(2)}$ van der Waals interactions energies between PVA and CD1 in Kcal/mol

N°	CD1 proton acceptor and PVA donor		B3LYP/6.31G(d)	M05-2 × 6.31G(d)
1	σ C62–H139	σ* H42–C19	1.65	1.63
	σ H42–C19	σ* C62–H139	3.10	3.15
2	σ C68–H146	σ* H44–C19	1.52	1.52
	σ H44–C19	σ* C68–H146	2.91	2.97
3	σ C74–H153	σ* H32–C7	2.23	2.27
	σ H32–C7	σ* C74–H153	2.34	2.32
4	σ C76–H155	σ* H52–C23	1.08	1.09
	σ H52–C23	σ* C76–H155	2.66	2.71
5	σ C80–H160	σ* H46–C20	2.21	2.20
	σ H46–C20	σ* C80–H160	2.84	2.89
6	σ C82–H162	σ* H53–C23	2.19	2.20
	σ H53–C23	σ *C82–H162	2.66	2.91
7	σ C94–H176	σ* H36–C12	1.55	1.58
	σ H36–C12	σ* C94–H176	1.95	2.17
8	σ C95–H178	σ* H37–C14	1.50	1.54
	σ H37–C14	σ* C95–H178	2.11	2.12
9	σ C101–H184	σ* H36–C12	1.90	2.00
	σ H36–C12	σ* C101–H184	2.15	1.97

Table 6 $E^{(2)}$ van der Waals interactions energies between PVA and CD2 in Kcal/mol

	CD2 proton acceptor and PVA donor		B3LYP/6.31G(d)	M05-2 × 6.31G(d)
10	σ C227–H307	σ* H45–C20	2.65	2.65
	σ H45–C20	σ* C227–H307	2.40	2.47
11	σ C233–H146	σ* H26–C1	1.99	1.98
	σ H26–C1	σ* C233–H146	2.92	2.99
12	σ C239–H314	σ* H30–C6	3.21	3.18
	σ H30–C6	σ* C239–H314	3.76	3.79
13	σ C245–H328	σ* H31–C6	2.00	1.98
	σ H31–C6	*σ C245–H328	3.14	3.18

(b) Van der Waals interactions

Energies associated with Van der Waals interactions are quite small and the cumulative effect of this small bonding can be enormous. Usually, they are about 0.5 and 1 kcal/mol per atom pair. In our case, when the complex is formed a large number of PVA and βCD atoms are in Van der Waals interaction. Thus, vinylic hydrogen atoms (H32), (H36) and (H37) are in Van der Waals contact with hydrogen atoms of C–H bonds of β-CD1 molecule. In addition to these short-range interactions, two hydrogen atoms (H52, H53) of H_3(C23) group and hydrogen atom (H46) of H_3(C20) group and one hydrogen atom (H42) of H_3(C19) group of the PVA molecule interacts also through van der Waals interaction with some C–H bond of the β-CD1 molecule. While, the hydrogen atoms of C–H bonds of the β-CD2 molecule are in van der Waals interactions with: (i) the second hydrogen atoms (H45) of H_3(C20) group, (ii) one hydrogen atom (H26) of H2(C1) group of cyclohexen, (iii) hydrogen atoms H(30) and (H31) of H_2(C6) group of cyclohexen. These values of van der Waals interactions obtained with both B3LYP/6-31G(d) and M056 × 2/6-31G(d) methods vary between 1 and 3.8 kcal/mol which can be considered as underestimated values. In despite this one can safely provide significant quantitative information on this interaction. Thus, Based on the values of $E^{(2)}$ stabilization energies (Tables 5, 6) which show in almost all cases except the interaction N°10 that $E^{(2)}$ of [σ C–H of PVA → σ* C–H of CD1] is

superior than [σ C–H of CD1 → σ* C–H of PVA. Hence, these results indicate that C–H bonds of PVA molecule act as donor and both CD molecules act as acceptor in the interaction between them.

Conclusion

Our work is focused on the study of optimization inclusion in complex PVA/βCD with stoichiometry 1:2, starting from the complex 1:1 using quantum calculations. The results suggest that the stability of the complex is due to hydrogen bond between the two cyclodextrins. And the study using NBO analysis show also that Van der Waals interaction constitutes a major driving force in the complexation of PVA into the two cavities of βCDs. Moreover, the two [M05-2X/6-31G*:PM3MM] and [B3LYP/6-31G*:PM3] ONIOM2 methods gives almost the same results which are in agreement with experimental data.

Solvent effect that is not considered in this study plays probably an important role of complexes between PVA and natural or modified cyclodextrins. Nevertheless the present work represents a preliminary result which gives an idea of inclusion process of PVA in CDs.

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