SEMI-EMPIRICAL PM3 STUDY ON COMPLEXATION OF β-CYCLODEXTRIN WITH 5-FLUCYTOSINE

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The synthesis of the β-cyclodextrin-5-flucytosine inclusion complex in aqueous media has been recently reported, the characterization of the complex proving the complete inclusion of the 5-flucytosine molecule into the β-cyclodextrin cavity. Still, the type of interactions that stabilize the supramolecule and the structure of the complex have been poorly described. The present paper focuses on the use of quantum semi-empirical PM3 calculations to establish the equilibrium molecular geometry of a stable inclusion complex formed of 5-flucytosine and β-cyclodextrin. Two types of stable complexes were obtained, with a small difference (~1 kJ) between the stabilization energies. In both cases, the major driving forces are the hydrogen bonds. The most stable of them, in vacuum, is a complex with a 5-flucytosine molecule located outside the β-cyclodextrin cavity. The second one, containing a 5-flucytosine molecule included into the cyclodextrin cavity, was identified as a real complex, by previously reported ^{1}H-NMR data. Despite the stabilization energies, the formation of the second inclusion complex with 5-flucytosine inside the cyclodextrin cavity is attributed to the solvent effect.

Keywords: cyclodextrin, cyclic oligosaccharide, inclusion complex, molecular geometry, driving force

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six, seven or eight α-1,4-linked glucose residues (Fig. 1), forming a truncated cone shape of 7.9 Å height, which is their characteristic feature. Because of their particular structure, the CDs present a hydrophilic character at the edges of the truncated cone, and a hydrophobic character in the inner cavity. The presence of the inner hydrophobic cavity recommends the CDs as receptors (host molecules) able to include in the cavity a wide class of molecules, such as organic, inorganic polymers and biomolecules. The non-covalent bonds assure the stability of the inclusion complexes. The complexation with CDs induces specific modifications of the physico-chemical properties of the 'guest' molecules, particularly in terms of water solubility and solution stability.[1] These types of complexes (host–guest) can be used for different applications, such as drug delivery systems,[2-4] catalysis,[5] separation technology,[6] etc. Furthermore, the CDs, considered as a very important model for enzyme–substrate[7] interactions, can be included into a variety of other polymeric materials, such as gel microparticles.[8]

The driving forces leading to complexation are numerous, varying from van der Waals forces and hydrophobic effect to dipole–dipole interactions. Liu *et al*.[9] have pointed out the importance of charge transfer interactions for α-CD complexation with several molecules, such as nitrobenzene or benzoic acid. Recently, the theoretical analysis of charge transfer in cyclodextrins complexation has been experimentally confirmed.[10] The mechanism of charge transfer interaction can be summarized as follows: when a supermolecule is built up from two components, the mixing of the filled orbital of the first molecule with the vacant orbitals of the second occurs, leading

to a charge transfer between the two molecules. Hence, an attractive force between the two components arises. Due to their big number of atoms, CDs and their inclusion complexes are always a challenge for computational chemistry, which can identify and predict different types of intermolecular interactions and conformational changes produced during complexation. The first equilibrium geometries were obtained with methods reaching convergence in a relatively short time, such as molecular mechanics (MM),[11] molecular dynamics (MD)[12] and Monte Carlo simulation (MC).[13] The quantum mechanical methods have the advantage of providing information on the electronic structure of the system and hence, a better understanding of the inclusion structure. Once the computer resources enhanced, computer simulation by quantum semi-empiric calculation could be applied in cyclodextrin chemistry. Further on, a large class of quantum semi-empirical methods, such as AM1 (Austin Method 1) and PM3 (Parametric Method 3), where used with good results. The last method, considered optimal as it deals better with the hydrogen bonds,[14] was successfully applied in cyclodextrin chemistry.[15,16]

5-flucytosine (FC) is an old antifungal agent.[17] The interest for this drug increased, due to the new therapeutic applications in some tumor treatments, especially in colorectal carcinoma.[18] The complexation of 5-flucytosine (FC) with β-cyclodextrin offers the possibility to improve FC solubility in aqueous media, without chemically changing the original structure, thus enhancing the potential biomedical applications, as due to toxicity reduction. As far as we know, the only approach to β-CD-FC complexation was reported by M. Spulber and coworkers,[19,20] no quantum mechanical study having ever been initiated on this type of complex.

This paper deals with the interaction between FC and β-CD molecules by means of quantum mechanical calculation PM3, for examining in detail the insertion pathways, and for determining the intimate configuration of the obtained inclusion complex.

EXPERIMENTAL

Computational method

All theoretical calculations were performed using version 7.52 of the HyperChem software package.[21] For all described systems, a full geometry optimization was performed at PM3 level,[22,23] with the convergence limit SCF = 10^{-5} and a gradient RMS = 10^{-2} kcal/Å mol, using the Polak-Ribiere conjugate gradient.

Due to the large dimensions of the molecular structures, vibration frequency analysis was performed to characterize the local stationary points as true minima. Calculations were carried out in the gas phase, the effects of the solvent being not taken into account.

The initial structures of β-CD and FC, built up by the graphic interface of HyperChem, were fully optimized by the PM3 calculation method. β-CD was built up with α-D-glucopyranose residues (contained in the database of HyperChem software), that were connected with other residues by α-(1,4)-glycosidic oxygen bridges. A comparison of the molecular parameters with the values already reported in literature[24-26] led to the conclusion that molecular geometries present satisfactory energetic minima.

The optimization of the CD molecular geometries is a multiple minima problem. The value of the entire surface potential is very difficult to obtain, requiring large computational resources. That is why, a relatively fast method was developed[15] to identify the structure of the complex corresponding to the global minima on the potential surface energy. The first step of this method uses the glycosidic oxygen atoms from the CD structure to define the normal XY plane coordinates, so that the center of the plane will coincide with the origin of the coordination system. In the second step, the guest molecule is placed on the Z-axis, where only a reduced number of different orientations of the guest molecule, relatively to the CD molecule, are taken into consideration. As already described in the literature,[27,28] the rotation of the guest molecule related to the CD cavity may be avoided due to the high CPU cost. The minimization process can automatically find the best rotational orientation of the substrate.

The coordinate system here used to define the process of complexation is shown in Figure 2. In the beginning, the glycosidic oxygen atoms of β-CD are placed onto the XY plane and their center is considered as the center of the coordination system. The primary hydroxyl groups of β-CD are orientated towards the positive direction of the Z-axis. The nitrogen from the secondary amino group NH (A2) of the FC ring and the primary amino group NH_2 (A1) of the FC substrate coincide with the Z-axis. The relative positions of both host and guest were measured by the Z-coordinate (Å) of the dummy atom "*****" located in the middle of the FC ring. Our method is based on the hypothesis of the drug molecule entrance into the CD inner cavity, as reported earlier. That is why, the guest is initially placed in the center of the CD cavity, at Z = 0. To search the favorable angular orientation

inside the β-CD cavity, the guest is rotated from 0 to 360° relatively to the YOZ position, with an angular phase θ = 45°. In each point, the molecular structure is completely optimized with PM3 calculations, without symmetry restriction. After obtaining several energetical local minima (θ_m), guest orientation at $\theta_m \pm 15^o$ is checked, to validate it as a global minimum. The minimal value of the potential energy obtained (θ_m (Z = 0)) is considered as the optimal angle for guest entrance into the CD cavity.

After θ_m determination, the guest is initially located on the Z-coordinate, at 10 Å, being shifted with a stepwise of 1 Å at θ_m = const. along the Z-axis, all through the host cavity, up to a distance of -10 Å. The minimal value of the stabilization energy for the θ_m and Z_m starting coordinates can characterize the equilibrium geometry of the β-CD-FC complex.

Two possible cases are considered. In the former one, FC is initially oriented with the primary amino group A1 towards the negative direction of the Z-axis (Fig. 2a), while, in the latter case, the primary amino group of FC is pointed towards the positive direction of the Z-axis (Fig. 2b).

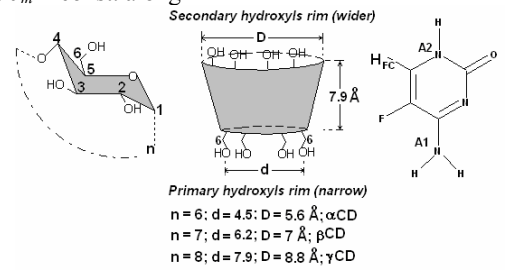

Figure 1: Truncated con shaped structures of CD molecules and FC structure

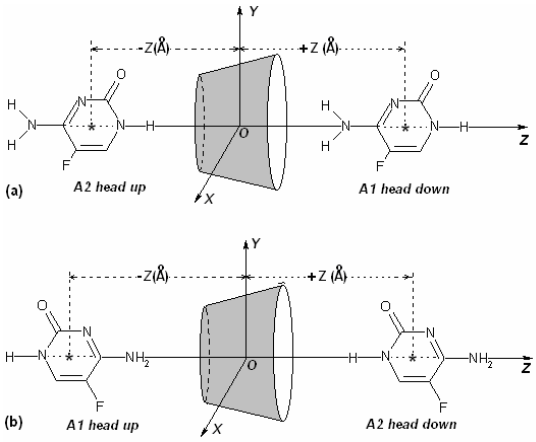

Figure 2: Molecular coordinates used for characterizing the approach of FC molecule to β-CD cavity. The primary amino group A1of FC pointed towards the negative (a) and positive (b) direction of the Z-axis

RESULTS AND DISSCUSSION

Identification of complex conformations

In the present paper, the minimal energy of the molecular geometries was characterized by means of the stabilization energy (ΔE) between FC and the β-CD, according to eq. (1):

$$\Delta E = E_C - \left(E_{CD} + E_{FC}\right) \quad (1)$$

where E_C, E_{FC} and E_{CD} represent the formation heat of the complex, of the free substrate and of the free CD, respectively.

The magnitude of the energy change variation indicates the nature of the driving force involved in the complexation process. The more negative is the stabilization energy, the more thermodynamically favorable is the formation of the inclusion complex.

An important parameter, which characterizes the complexation process, is the deformation energy of the CD (ΔE_d), a measure of the conformational effort made during complexation (eq. 2):

$$\Delta E_d = E_{sp}^{opt} - E_{CD} \quad (2)$$

where E_{sp}^{opt} is the single point calculation energy of β-CD characteristic for the configuration considered from the optimized complex geometry. The guest molecule is initially placed at coordinate Z = 10 Å. As

presented in Figure 2 a,b for the movement of the guest molecule within the ±10 Å interval, four different approaches of the FC entrance into the β-CD cavity are taken into consideration, depending on the direction of the FC primary amino group, and also on the nature of the β-CD rim that encounters the FC molecule. The configuration with the primary amino group A1 of FC as the head of molecule is named the A1 head, while that with the secondary amino group NH of FC (A2) as head is named the A2 head. Consequently, two different approaches are available to the cyclodextrin cavity for each of the FC heads: "head up" and "head down", defined as in Figure 2 a,b. The stable molecular equilibrium geometries have the same names as the approach types.

Scanning the stabilization energy for each angle orientation at the starting point Z = 0 leads to exclusively negative values, which reveals that the energy of the complex is consistently lower than the sum of the isolated host and guest molecule energies. This indicates a high probability of complex formation, with FC completely included in the β-CD cavity. As presented in Figure 3 a,b, only a global minimum of the stabilization energy can be separately identified for both orientations of the FC molecule at the starting Z = 0: with amino group A1 of FC towards the negative direction of Z (Fig. 3a, $\theta_{m1} = 90^o$) and towards the positive direction of Z (Fig. 3b, $\theta_{m2} = 105^o$). The following structures with starting values $Z \neq 0$ contain only FC molecules oriented at starting $\theta_{m1,2}$ = const. According to Figure 4 a,b, the maintenance of $\theta_{m1,2}$ constant and the variation of the starting parameter Z induce the formation of molecular structures with negative values of stabilization energy, which suggests that the FC approach with both amino groups A1 and A2 by both primary and secondary cavity rims of β-CD is favorable. Hence, the shape of the stabilization energy variation with different Z parameters, starting at fixed $\theta_{m1,2}$, is unusual for this type of complexes. As illustrated in Figure 4 a,b, the most favorable situation occurs when FC enters with both amino groups A1 and A2 through the secondary β-CD rim, and the most stable complexes will be named, respectively, A1 head down and A2 head down.

The molecular structure of A1 head down (Fig. 5 a,b), with starting parameters Z = 0 Å and $\theta = 90^o$ generated by PM3 optimization, presents the most stable molecular geometry when the primary amino group A1 is oriented in the negative direction of Z (ΔE = 30.78 kJ/mol).

Driving force of complex formation

An important factor in complex stabilization is the ability of cyclodextrins to act as an acid or weak Lewis base.[29] This phenomenon can induce complex stabilization and is in close relationship with the energies of HOMO and LUMO orbitals of the two molecules – the host and the guest. In Table 1, a non-zero Mulliken population on the β-CD molecule can be observed, suggesting a possible charge transfer between the host and guest molecules. The value of the transferred charges is rather low and its contribution to the complex stabilization is really weak and can be neglected.

As illustrated in Figure 5 a,b, the formation of two hydrogen bonds in this complex is possible. The first hydrogen bond, 2.51 Å in length, is established between the hydrogen atom of the secondary HO^2 of β-CD and the double bonded oxygen atom from the FC structure. The other hydrogen bond, 2.9 Å in length, is formed between the hydrogen atom of the primary amino group and the glycosidic oxygen atom of β-CD. These hydrogen bonds generate attractive forces, causing complex stabilization, and can be considered as the driving forces of the complexation process.

In the A2 head down (Fig. 5 b,c), the FC molecule enters the β-CD cavity with a secondary amino group through the secondary cavity rim. A lower stabilization energy is obtained for the starting parameters Z = 7 and $\theta = 105^o$, and the negative value of 32.07 kJ/mol obtained is close to that of the A1 head down (30.78 kJ/mol). Although the difference between the stabilization energy of the A1 and A2 head down complexes is small (1.29 kJ), the two possible structures of the complex are very different. In the A1 head down complex, the FC molecule is entirely included in the cyclodextrin cavity while, in the A2 head down, the FC molecule is completely outside the cyclodextrin cavity. The A2 head down is stabilized by two hydrogen bonds.

The former, a 1.79 Å long bond, is established between the oxygen atom of the FC molecule and the hydrogen atom of HO^2 of the secondary cyclodextrin rim. The latter,

the 1.8 Å-long hydrogen bond, is formed between the hydrogen atom of the secondary amino group A2 of FC and the oxygen atom of the HO^3 group contained in the same glucopyranose residue.

In the A2 head down, the nontrivial charge on β-CD is reversed compared with the A1 head down. The charge transfer is a little bit higher than that of the A1 head down (Table 1), but it is still too low for having a real contribution to the complex stabilization, so that it can be neglected. In fact, the charge transfer interaction is of the van der Waals type.[30-32] The A2 head down is unlikely to confirm a charge transfer interaction directly between the β-CD skeleton and the substrate, since the FC molecule is outside the cyclodextrin cavity. Consequently, a change of behavior in the charge transfer in the two complexes discussed reflects only the change in the van der Waals interactions, through orientation of the guest molecule. The literature[9] shows that the charge transfer should be higher than the values here observed (at least 0.01 e), for influencing the complex stabilization.

The polarity of the β-CD cavity decreases after the guest enters the cavity. As listed in Table 1, the dipole moment of the A1 head down complex is of 5.834 De, 1.085 lower than the dipole moment for native β-CD. The dipole moment of the A2 head down, lower than the sum of the dipole moments of the host and guest molecules, is 1.1 De higher than the dipole moments of native β-CD, and 2.18 De higher than the dipole moment of the A1 head down complex. One can therefore conclude that the dipole moment values show a strong correlation with the complexation behavior.

Table 1
Molecular parameters obtained by semi-empirical PM3 calculation of A1 and A2 head down complexes

Parameter	FC	β-CD	A1 head down	A2 head down
E (kJ/mol)	-229.72	-6092.72	-	
E_C (kJ/mol)	-	-	-30.78	-32.07
Ed (kJ/mol) of β-CD in complex structure	-	-	1.58	1.34
LUMO (eV)	-1.10	1.47	-1.10	-1.11
HOMO (eV)	-9.67	-10.89	-9.67	-9.71
HOMO-LUMO	-8.54	-12.37	-8.56	-8.59
Mülliken charges on β-CD in complex structure	-	-	+0.002	-0.005
Dipole (De)	4.141	6.915	5.83	8.01
Length of hydrogen bonds (Å)	-	-	O_{FC}, HO^2 = 2.51 NH_2, O_{CD} = 2.95	O_{FC}, HO^2 = 1.79 NH, OH^3 = 1.80

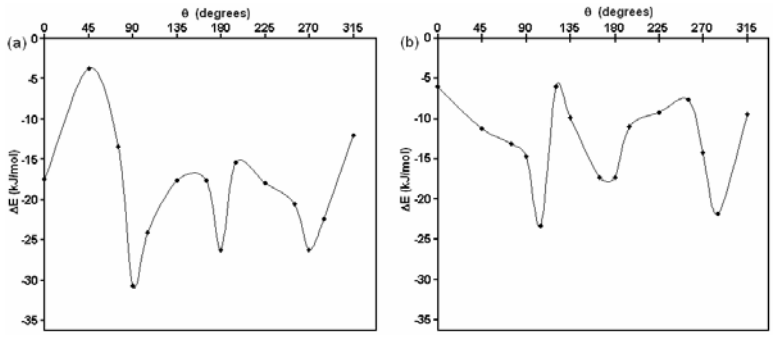

Figure 3: Dependence of stabilization energy on θ angle, at a starting distance $Z = 0$ Å. The primary amino group A1of FC pointed towards the negative (a) and positive (b) direction of the Z-axis

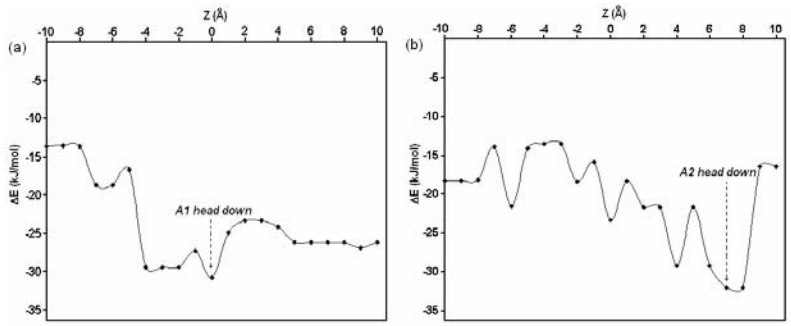

Figure 4: Dependence of stabilization energy on Z distance at starting $\theta_{m1} = 90^{o}$ (a) and $\theta_{m2} = 105^{0}$ (b). The primary amino group A1 of FC pointed towards the negative (a) and positive (b) direction of the Z-axis

M. Spulber *et al*.[19] clearly showed that, in the β-CD-FC complex, the FC molecule is completely included in the β-CD cavity and that the stability constant is of 70 M^{-1}. The synthesis was performed in aqueous media and, considering the low solubility of FC in water (~0.081 M at 25 °C),[33] we can conclude that the FC molecule is more compatible with the hydrophobic cyclodextrin inner cavity than with the aqueous media.

PM3 calculations indicate the formation of two different types of inclusion complexes. The small difference between the stabilization energies of the above-mentioned complexes, equal to 1.29 kJ, does not justify the experimental predominance of the A1 or A2 head down complex. The contrast between the similarity of the complexes' stability and the predominance of the A1 head down complex during the experimental phase in aqueous media suggests that the solvent media has a decisive influence upon the complex structure. The dependency of the complex structure on the solvent media was already reported in literature, in a computational study performed by Guo *et a1*.[34] In the A2 head down complex, the FC molecule is outside the CD cavity (Fig. 5d) and exposed to aqueous media while, in the A1 head down complex, FC exposure to the water environment is minimal, because of the FC molecule entering the hydrophobic β-CD cavity (Fig. 5b). In the A1 head down complex, the primary amino group NH_2 of FC takes part to hydrogen bond formation, as experimentally revealed[19] by ^{1}H-NMR spectra performed in THF.

According to literature,[2,3,38] the chemical shifts of the H^3 and H^5 proton signals, located in the cyclodextrin cavity, are a very good index of complex formation, due to the low distance between them and the other atoms of the guest molecule.[36] As shown in Figure 6, the FC molecule is not parallel to the Z-axis inside the β-CD cavity. Due to this orientation, the H_{FC} hydrogen atom of FC is very close to the H^3 one, located inside the β-CD cavity, the perturbation caused by this approach being experimentally evidenced[19] in the ^{1}H-NMR spectra performed in THF by a remarkable downfield shifting of the H_{FC} proton and an upfield shift of the H^3 proton of β-CD. As shown in Figure 5d, in the A2 head down complex, these chemical shifts can not be explained.

In conclusion, in the CD-FC inclusion complex, the FC molecule is located inside the inner cavity of β-CD, as experimentally confirmed by the chemical shift of the protons of the primary amino group, the H_{FC} hydrogen atom of the FC molecule and the H^3 proton of the β-CD molecule. The molecular structure of the complex was computed by PM3 semi-empirical calculation and the experimental data were explained by the formation of two hydrogen bonds and the steric interaction between the H_{FC} of FC and the H^3 atom of β-CD.

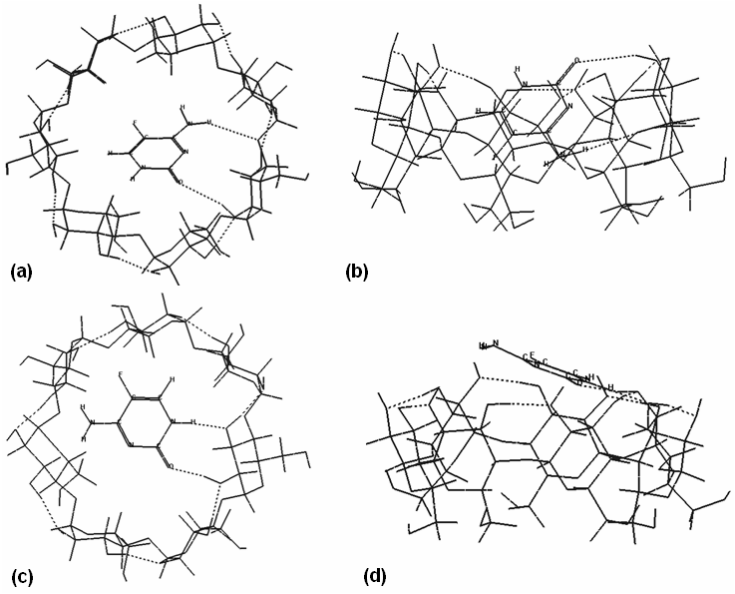

Figure 5: Equilibrium molecular geometries obtained by PM3 calculation of complexes A1 head down (a, b) and A2 head down (c, d)

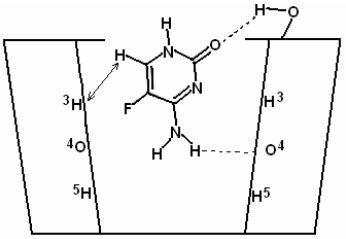

Figure 6: Schematic structure of A1 head down inclusion complex (the real molecular dimensions are neglected)

CONCLUSIONS

The inclusion process between 5-flucytosine and β-cyclodextrin and the possible obtaining of new stable structures were studied by the quantum mechanical PM3 method. Two types of stable complexes were identified: an inclusion complex and another complex, with the 5-flucytosine molecule outside the β-cyclodextrin cavity. Several hydrogen bonds are formed in both complexes, which can act as driving forces towards complex formation. The real structure of the inclusion complex was selected according to previously reported ^{1}H-NMR experimental data. Further characterization of the structures and the stability of these complexes can be performed by taking into consideration the solvent effect in process calculation.

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