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Inclusion Complex Formation of β–Cyclodextrin with the Nonsteroidal Anti–Inflammatory Drug Flufenamic Acid: Computational Study

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Structural study and thermodynamics of complexation between β-cyclodextrin (β-CD) and flufenamic acid (FFA) are explored by means of several quantum chemical methods. The different orientation modes of FFA in the cavity of β-CD are studied. PM3MM, ONIOM2 and DFT methods show that the complex FFA/β-CD in A orientation is found to be the most favorable energetically. The statistical thermodynamic calculations at 1 atm and 298.15 K reveal that the complexation process is exothermic and enthalpically driven. Finally, the calculated chemical shifts of free FFA and its complex at B3LYP/6-31G(d) level by employing the Gauge-Including Atomic Orbital (GIAO) method are in good agreement with NMR experimental data.

Keywords: β-Cyclodextrin, flufenamic acid, hydrogen bond, inclusion compounds, quantum chemical calculations, thermodynamics.

Образование комплексов включения β–циклодекстрина с нестероидным противовоспалительным лекарственным средством – флуфенамовой кислотой: квантово–химическое исследование

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Проведено структурное исследование и изучена термодинамика комплексообразования между β-циклодекстрином (β-CD) и флуфенамовой кислотой (FFA) с помощью квантово-химических методов. Исследованы различные способы ориентации FFA в полости β-CD. Методы PM3MM, ONIOM2 и DFT показывают, что комплекс FFA/β-CD в ориентации A оказывается наиболее энергетически выгодным. Статистические термодинамические расчеты при 1 атм и 298,15 K демонстрируют, что процесс комплексообразования является экзотермическим и энтальпически контролируемым. Наконец, расчетные химические сдвиги свободной FFA и ее комплекса на уровне B3LYP/6-31G(d) с использованием метода калибровочно-инвариантных атомных орбиталей (GIAO) хорошо согласуются с экспериментальными данными ЯМР.

Ключевые слова: β-Циклодекстрин, флуфенамовая кислота, водородная связь, комплексы включения, квантово-химические расчеты, термодинамика.

Introduction

Fenamates such as flufenamic acid, tolfenamic acid, mefenamic acid, meclofenamic acid and niflumic acid are derivatives of anthranilic acid.[1] Several pharmacological studies were carried out for this class of nonsteroidal anti-inflammatory drugs (NSAIDs) to evaluate the anti-inflammatory, analgesic and antipyretic properties as well as their inhibitory activity.[2,3] The poor water solubility of flufenamic acid (FFA) causes difficulties related to the design of pharmaceutical formulations for oral or parenteral route administration, leading thus to low oral bioavailability.[4] Complexation with cyclodextrins is an approach that can be used to circumvent this problem by improving their solubility.[5,6]

Cyclodextrins (CDs) are a family of water-soluble natural cyclic polysugars consisting of (α-1,4)-linked α-D-glucopyranose units, that act as cages-like molecules. The most known and studied members of this family are α-CD, β-CD and γ-CD which can complex a broad array of organic molecules through host-guest inclusion systems. CDs are widely used in various fields such as food technology, pharmaceutical, cosmetics and textile industry,[7-13] their *cone*-shaped structures enclose a hydrophilic external surface and a relatively hydrophobic inner cavity, resulting in the ability of CDs to encapsulate small hydrophobic organic guest molecules.

The predominant driving forces involved in drug-CD complex formation are van der Waals interactions, hydrogen bonds, hydrophobic interactions between the host and guest molecules and entropy released by uncomplexed water molecules from the CD cavity.[14-17]

Among these macrocycles, β-CD exhibiting the lowest aqueous solubility is the most commonly used as a cheapest molecular host because its cavity diameter can bind efficiently various molecules such as hormones, [18,19] metals[20] and vitamins.[21,22]

In the last decades, experimental techniques including Proton Nuclear Magnetic Resonance spectroscopy (^{1}H NMR) used in combination with computational investigations, have been dedicated to the study of inclusion complexes of CDs.[23,24] There are several computational methods used in molecular modeling studies such as semi-empirical methods[25-35] hybrid ONIOM method (our Own N-layer Integrated Orbital Molecular mechanics),[36-38] Hartree Fock (HF),[39-41] density functional theory (DFT)[42-46] and Monte Carlo simulation.[47,48] Among these methods, semi-empirical calculations using PM3MM level of theory[49] is generally acceptable and used for the structural assignment of CD inclusion complexes.

Recently, C.G. Floare *et al.*[50] have studied the complexation process between flufenamic acid and tolfenamic acid with β-CD by ^{1}H NMR spectroscopy.

Only a few theoretical studies on β-CD complexes formation with NSAIDs drugs derived from fenamic acid have been reported in the literature.[51-54]

In the present work, we study the encapsulation of FFA into β-CD (Figure 1) by means of molecular modeling, using the semi-empirical method PM3MM, the ONIOM2 (B3LYP/6- 31G(d):PM3MM) hybrid technique and DFT approach.

Computational Methods

The initial structure of the FFA was constructed using Hyperchem 7.5 molecular modeling package.[55] The starting geometry of β-CD was taken from Chem-Office 3D ultra (version 10, Cambridge Software).[56] Then two structures, FFA and β-CD, were optimized by means of PM3MM semi-empirical method prior to using Gaussian09[57] for all relevant calculations. The coordinate system used to define the process of complexation is shown in Figure 2. The method of Liu *et al.* was applied to locate the lowest energy minimum of the FFA/β-CD inclusion complex.[28]

The glycosidic oxygen atoms of β-CD are placed in XY plane and their center is defined as the center of the whole system. FFA approaches and passes through the cavity of β-CD from +Z to –Z direction. The guest is initially located at a Z coordinate of 10 Å and is moved through the host cavity along the Z axis to –10 Å with a step of 1 Å. For each step, the geometry of the complex is fully optimized by PM3MM without symmetry 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, clock wisely circling around Z axis, at 20° intervals from 0° to 360°.

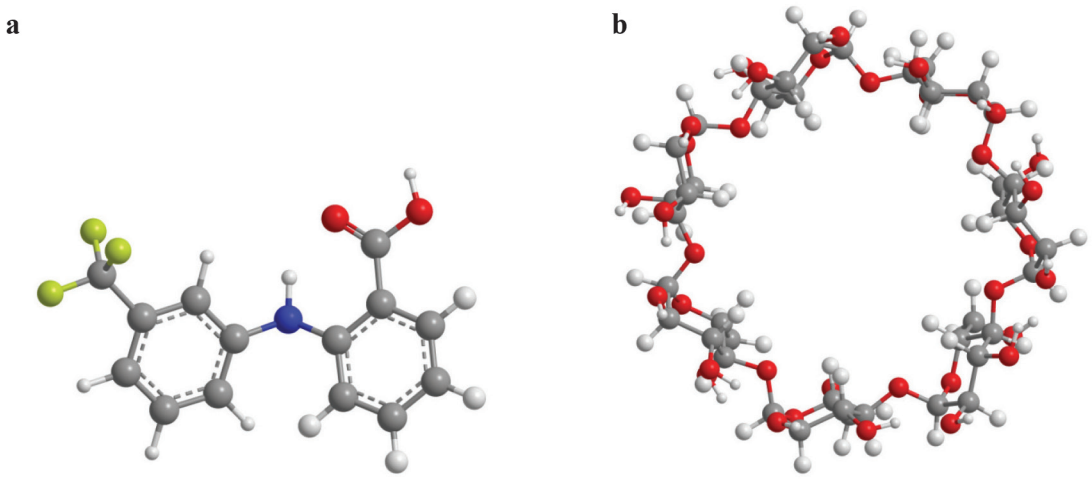

Figure 1. Geometrical structures of FFA (a) and β-CD (b).

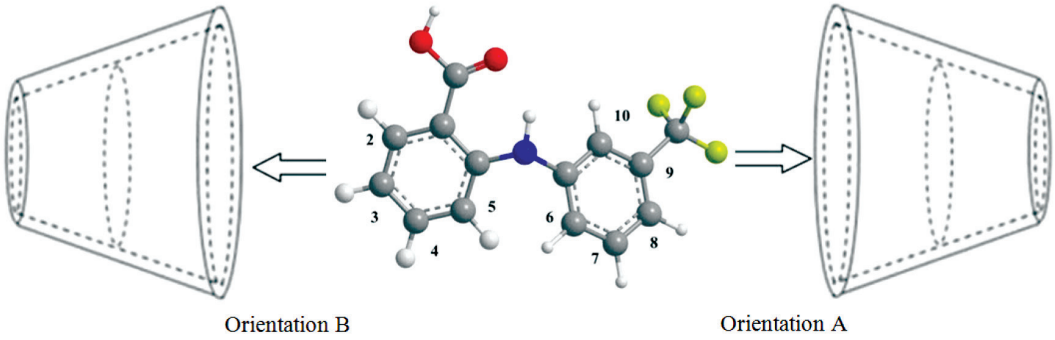

Figure 2. Coordinate systems defining the process of inclusion for FFA/*β*-CD, A and B orientations.

To quantify the interaction between host and guest in the optimized geometries, we have evaluated the complexation energy (ΔE) using the following formulae (Equation 1)

$$\Delta E = E_{complex} - (E_{free\,FFA} + E_{free\,\beta\text{-}CD}), \quad (1)$$

where $E_{complex}$, $E_{free\,\beta\text{-}CD}$, and $E_{free\,FFA}$ represent, respectively, the total energy of the complex, the free optimized *β*-CD and the free optimized FFA energy.

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 (Equation 2)

$$E_{deformation}(component) = E[component]_{sp}^{opt} - E[component]_{opt}. \quad (2)$$

Then, different levels of calculation were made using DFT and hybrid method (ONIOM2) in vacuum and aqueous solution in the aim to perform a more accurate inspection on the geometry and electronic structure of FFA/*β*-CD complex.

At last, based on ONIOM2 optimized geometries, ^{1}H NMR calculations were carried out to quantify the chemical shifts of protons of *β*-CD, FFA and their inclusion complex.

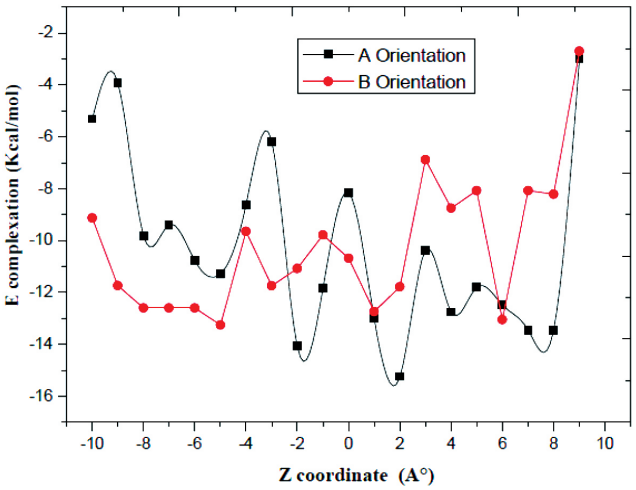

Figure 3. Complexation energy of FFA/*β*-CD in the gas phase calculated for both orientations at different positions of Z-axis using PM3MM method.

Results and Discussion

Conformational Energy Search

Conformational energy searching enabled us to identify the most energetically preferred conformations corresponding to the lowest energy structures. The most stable conformers found for A and B orientations by PM3MM method are shown in Figure 3. To account for solvation effects, CPCM water solvent model was used to simulate the aqueous environment.

The energy of the complex decreases as the guest molecule penetrates the *β*-CD cavity, suggesting that weak intermolecular interactions cooperatively contribute to the stable complex formation. The negative stability energies in all positions show that the complex formation is highly probable. In the range from –10 Å to –3 Å, structures in B orientation are more stable than A orientation, while the structures in A orientation are more stable within the range from –2 Å to 10 Å, except for 0 Å and 6 Å configurations. When the distance between the reference atom and the plane of glycosidic oxygen atoms of *β*-CD is 2 Å and –5 Å for A and B configurations with ΔE=–15.25 kcal/mol and –13.23 kcal/mol, respectively, the energy of the system is minimal in vacuum, thus indicating the formation of the supramolecular complexes, inclusion complex of FFA/*β*-CD for A model is the most thermodynamically favorable due to its higher negative value of ΔE, which is in good agreement with the predicted mode of inclusion process by the experimental study.[50]

Thermodynamics

The statistical thermodynamics calculations[58,59] were performed using harmonic frequency analysis in PM3MM method for the most stable structures which correspond to true minima on the potential energy surface. The frequencies analyses were then used for the evaluation of the thermodynamic parameters, such as enthalpy changes ($H°$), entropy contribution ($S°$) and Gibbs free energy ($G°$), for the statistical thermodynamic parameters in binding process of FFA with *β*-CD at 298.15 K and 1 atm were summarized in Table 1.

The negative enthalpy changes indicate that the inclusion complexation process of FFA with *β*-CD is exothermic. The enthalpy change for the A configuration is more negative than that of B configuration pointing out that both the inclusion processes are enthalpically favorable in nature.

Table 1. Energetic terms and thermodynamic parameters of FFA/*β*-CD complexes calculated at PM3MM level.

	FFA	*β*-CD	A orientation	B orientation
		In vacuum		
E (kcal/mol)	–195.68	–1449.15	–1660.08	–1658.06
Δ*E* (kcal/mol)			–15.25	–13.23
$E_{deformation}$ (FFA)			0.64	0.31
$E_{deformation}$ (*β*-CD)			–5.46	–5.25
H° (kcal/mol)	– 46.67	–660.68	–719.12	–718.51
Δ*H*° (kcal/mol)			–11.91	–11.15
G° (kcal/mol)	–87.78	–783.68	–859.95	–866.60
Δ*G*° (kcal/mol)		0.07	11.49	4.86
S° (kcal/mol)	–0.29		–78.09	–53.74
Δ*S*° (kcal/mol)			– 0.28	–0.29
		In water		
E (kcal/mol)	–200.09	–1482.26	–1701.49	–1697.95
Δ*E* (kcal/mol)			–19.14	–15.60
$E_{deformation}$ (FFA)			0.64	0.31
$E_{deformation}$ (*β*-CD)			–5.46	–5.25

In addition, it can be seen that the entropy changes (Δ*S*) of A and B configurations are also both negative, therefore suggesting that the formation of the inclusion complexes is an enthalpy-driven process. The formation of all of the complexes is non-spontaneous process because of the positive Gibbs free energy changes of complexation.

The complexation energies of FFA/*β*-CD for A and B configurations in vacuum were –15.25 kcal/mol and –13.23 kcal/mol, respectively. In water, the complexation energies become –19.14 kcal/mol for A configuration and –15.60 kcal/mol for B configuration leading to a larger energy difference of 3.54 kcal/mol when compared to vacuum.

ONIOM Calculations

To gain a better understanding of molecular recognition between the guest and the host, we applied ONIOM2 method. 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 FFA was treated at a high level of calculation using B3LYP and M05-2X functionals in conjunction with the 6-31G(d) basis set. The results of the ONIOM2 study are summarized in Table 2. It is interesting to note that the complexation process in the A orientation is more favorable than the B orientation both in vacuum and in water, which is in agreement with previous results obtained with PM3MM method.

Hydrogen Bonding Analysis

Hydrogen bonds are a fundamental specific interactions because they play a major role in a wide variety of materials in several areas, particularly physics, chemistry and biology.[60,61] A structural analysis is performed to study the effect of hydrogen bonds on the stability of the inclusion complexes. As shown in Figure 4, for A orientation, the guest is totally encapsulated in *β*-CD cavity. The structural analysis of A orientation shows the presence of one hydrogen bond formed between hydrogen atom H (173) of carboxylic group oxygen of FFA and interglycosidic oxygen atom O (56) of *β*-CD with a distance of 1.82 Å.

In the case of B orientation, no H–bonds were found and the guest molecule is partially encapsulated in *β*-CD cavity, this explains why the binding energy of the inclusion in the A orientation is lower than that of the B orientation.

Table 2. Relative energy for the optimized structures of complexes FFA/*β*-CD in both orientations as calculated by ONIOM2 method.

*E (*kcal/mol)	A orientation	B orientation	Δ*E*
	In vacuum		
E_{ONIOM} (B3LYP/6-31G(d):PM3MM)	–656762.27	–656761.71	–0.54
E_{ONIOM} (M05-2X/6-31G(d):PM3MM)	–656706.87	–656706.69	–0.18
	In water		
E_{ONIOM} (B3LYP/6-31G(d):PM3MM)	–656794.47	–656792.73	–1.74
E_{ONIOM} (M05-2X/6-31G(d):PM3MM)	–656718.44	–656716.58	–1.86

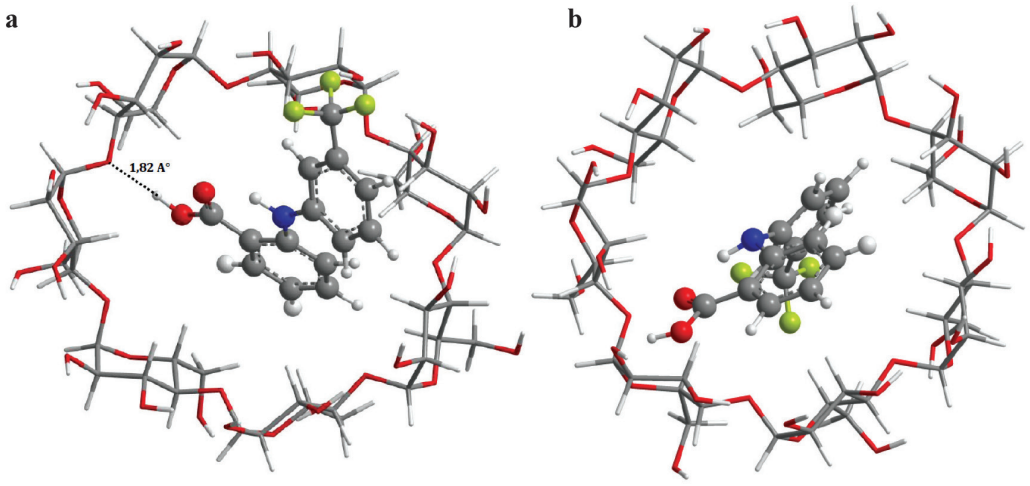

Figure 4. ONIOM2 optimized structures of FFA/*β*-CD complexes in the (a) A and (b) B orientations. Hydrogen bonds are indicated by dotted lines.

Natural Bond Order Analysis (NBO)

The natural bond order analysis (NBO) was performed at B3LYP/6-311G(d,p) level of theory, the stabilization energy ($E^{(2)}$) is used to characterize the interaction between occupied Lewis-type NBO orbitals and formally unoccupied non-Lewis NBO orbitals and is related to the delocalization trend of electrons from the bonding (BD) or nonbonding orbitals (LP) to the anti-bonding orbitals (BD*).[62,63] Stabilization energy ($E^{(2)}$) associated as a result of electron delocalization between donor NBO (i) and acceptor NBO (j) is estimated by following equation:

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

where q_i is the donor orbital occupancy; E(i) and E(j) are orbital energies of donor and acceptor NBO orbitals and F(ij) is the off-diagonal Fock matrix. The most important delocalization of electron densities are those arise from electron lone pairs (LP) of oxygen atoms as donors and OH bonds as acceptors.

The interactions energies clearly show that the shorter contact of the interaction, the larger value of $E^{(2)}$. By analyzing the second-order perturbation energies of the lowest energy complex in A orientation, it was found that the molecular recognition has been achieved through several interactions. The most important delocalization of electron densities are those arise from electron lone pairs (LP) of oxygen atoms as donors and OH bonds as acceptors. Their corresponding energies show that the $E^{(2)}$ values are increased with shortening hydrogen bonds distance d (O–H).

The interactions are in detail:

For A orientation. When FFA plays the role of donor, the important intermolecular hydrogen bond is observed between LP (2) O55 and σ*(1) O171 – H176 with energy equal to 12.70 kcal/mol.

On the other side, when FFA is an acceptor, the important H-bond is formed between LP (1) O172 and σ* (1) C15 – H93 with energy of 4.01 kcal/mol.

For B orientation. FFA plays the role of donor, the important intermolecular hydrogen bond is observed between LP (1) O 76 and σ* (1) O171 – H176 with energy equal to 9.92 kcal/mol.

On the other side, when the FFA is an acceptor, the important H-bond is formed between LP (2) O 171 and σ* (1) C53 – H116 with energy of 2.20 kcal/mol. The most important intermolecular contacts in the NBO analysis are represented in Figure 5.

More detailed analysis of intermolecular interactions using NBO is reported in Table 3.

Table 3. The electron donor orbital, electron acceptor orbital and the corresponding $E^{(2)}$ energies with NBO (B3LYP/6.311G(d,p)) calculations for A and B orientations.

Donor	Acceptor	$E^{(2)}$ (kcal/mol)
A orientation		
FFA proton donor and *β*-CD acceptor		
LP (1) O47	σ* (1) C157 – H161	1.02
LP (1) O55	σ* (1) O171 – H176	0.77
LP (2) O55	σ* (1) O171 – H176	12.70
LP (1) O63	σ* (1) C149 – F151	0.97
LP (2) O74	σ* (1) C169 – H173	1.60
β-CD proton donor and FF acceptor		
LP (1) O172	σ* (1) C15 – H93	4.01
LP (2) O172	σ* (1) C15 – H93	3.22
B orientation		
FFA proton donor and *β*-CD acceptor		
LP (1) O61	σ* (1) C166 – H170	1.51
LP (1) O76	σ* (1) O171 – H176	9.92
LP (2) O76	σ* (1) O171 – H176	5.97
β-CD proton donor and FF acceptor		
LP (2) O171	σ* (1) C53 – H116	2.20

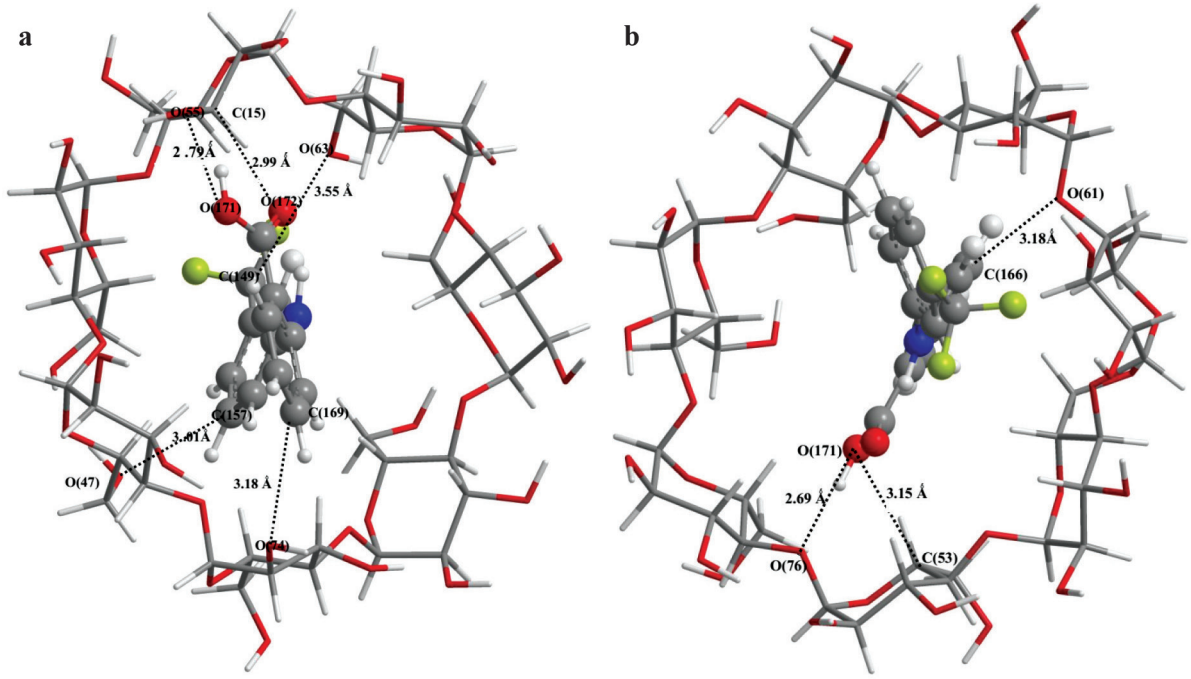

Figure 5. The significant intermolecular contacts using NBO analysis for the structures of FFA/*β*-CD complexes in the (a) A and (b) B orientations.

GIAO/DFT NMR Study

Based on ONIOM2 optimized geometries, the Gauge-Including Atomic Orbital (GIAO) method as implemented in Gaussian 09 was applied for ^{1}H NMR calculations[64,65] and by employing B3LYP functional and 6-31G(d) basis set with using corresponding TMS shielding calculated at the same theoretical level as the reference. The solvent effects have been investigated using the PCM method for water as a solvent (ε=78.39).

Experimental ^{1}H NMR chemical shifts obtained from C.G. Floare *et al.*[50] and our calculated values for the optimized structures referred to as (δ Exp) and (δ Calc) are summarized in Table 4.

Table 4. ^{1}H NMR chemical shifts (ppm) of FFA before and after complexation and comparison of experimental and theoretical ^{1}H chemical shifts of inclusion complex of FFA/*β*-CD calculated at the B3LYP/6-31G (d) level of the theory.

	FFA (ppm)		FFA/*β*-CD (ppm)	
Proton	δ_{free} (before inclusion) Calc.	δ Exp.	$\delta_{complex}$ (after inclusion) Calc.	Δδ ($\delta_{complex}-\delta_{free}$)
H2	7.45	7.78	7.67	0.22
H3	6.33	6.89	6.56	0.23
H4	6.84	7.29	7.62	0.78
H5	7.48	7.20	7.71	0.23
H6	7.51	7.26	7.80	0.29
H7	6.86	7.45	7.54	0.68
H8	6.65	7.40	6.84	0.19
H10	6.63	7.37	6.77	0.14
CH_3	–	–	–	–

From Table 4, the variation of the chemical shifts is observed for protons of aromatic ends of FFA indicating the possibility of presence of two types of complexes at ratio 1:1 involving the inclusion of both aromatic ring sides moieties inside the *β*-CD cavity in accordance with experimental results of ^{1}H NMR spectroscopy.

Conclusions

The inclusion process for FF acid with *β*-CD was studied according two orientations using quantum mechanics PM3MM, B3LYP level theory with 6-31G(d) basis set and ONIOM2 (B3LYP/6-31G(d): PM3MM) hybrid calculations. The minimum energy structure for each model was localized with PM3MM method. The affinity of these minimum energies structures was carried out with DFT and ONIOM methods. The DFT and ONIOM results show that the A orientation is preferred according to complexation energy. The analyses of the thermodynamic calculations indicate that the negative ΔG, ΔH and ΔS values suggest that the formations of *β*-CD/FF inclusion complexes in vacuo are a spontaneous and enthalpy-driven process. Finally, theoretical ^{1}H NMR chemical shifts correlate with the experimental findings.

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