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ORIGINAL ARTICLE

Quantum chemical calculations based on ONIOM and the DFT methods in the inclusion complex: doxycycline/2-O-Me-β-cyclodextrin

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Abstract A computational study of inclusion complexes of 2-methyl-βCD with Doxycycline tautomeric (enol and keto form) has been performed with several combinations of ONIOM hybrid calculations. The reliability of the ONIOM2 calculations at the integrated level, ONIOM2 (M05-2X/6-31G(d): M05-2X/3-21G*), ONIOM2 (M05-2X/6-31G(d):HF/3-21G*), ONIOM2 (B3LYP/6-31G(d):HF/3-21G*), ONIOM2 (B3LYP/6-31G(d):B3LYP/3-21G*) and ONIOM2 (B3PW91/6-31G(d):B3PW91/3-21G*) was examined. Their complexation, binding, deformation and stabilization energies, and geometrical data were compared with those of the target geometry structure optimized at the M05-2X/6-31G(d) level of theory. Mixed combinations ONIOM2 (M05-2X 6-31G(d):HF 3-21G*) and ONIOM2 (B3LYP 6-31G(d):HF 3-21G*) reproduces nearly the target geometry structure and provides realistic energetic results at a relatively low computational cost.

Keywords 2-Methyl-βCD(Crysmeb) · Doxycycline · NBO · M05-2X · DFT · ONIOM

Introduction

Cyclodextrins are cyclic oligosaccharides consisting of 6 (α-cyclodextrin), 7 (β-cyclodextrin), and 8 (γ-cyclodextrin) glucopyranose units linked by α-(1, 4) bonds [1, 2]. The form of cyclodextrin molecules resembles to a truncated cone with the secondary hydroxyl groups located at the wider edge of the ring and the primary groups on the narrow edge [3]. These parent molecules have been chemically modified through hydroxypropylation or methylation of the hydroxyl groups in order to improve their aqueous solubility and their ability to solubilise hydrophobic compounds [4]. Some of the most widely used β-cyclodextrin derivatives are (heptakis-2,6-di-O-methyl-β-CD (DIMEB), randomly methylated-β-CD (RAMEB) and partially methylated crystallized β–cyclodextrin (CRYSMEB) were investigated [5–10]. Virtually all derivatives have a changed hydrophobic cavity volume and also these modifications can improve solubility, stability against light or oxygen and help control the chemical activity of guest molecules [3, 4].

As well as the general indications for all members of the tetracycline group, doxycycline is frequently used to treat chronic prostatitis, sinusitis, syphilis, chlamydia, pelvic inflammatory disease [11, 12], acne, rosacea, and rickettsial infections [13–15].

The Doxycycline (both forms enol and keto)/methylated β-CD (Kleptose® Crysmeb) complexes were studied by means of one-dimensional 1H NMR, 2D ROESY experiments by Bakour. Thus, a stoichiometry of 1:1 had been determined for the complexation process and the authors revealed that the DOX molecule was included in the Crysmeb cavity by its aromatic ring. Doxycycline exists in two tautomeric forms (keto and enol) in which the keto–enol equilibrium in aqueous media is in favor of the enol form [16, 17]. Complexation is determined by hydrophobic interactions, hydrogen bonds, van der Waals interactions, conformational energy, dipole–dipole and ion–dipole interactions.

Dipolar interactions between H3, H5 of Crysmeb and 6-Me-protons, 7.8 and 9 of the doxycycline were observed [16, 17]. The objective of inclusion is to protect

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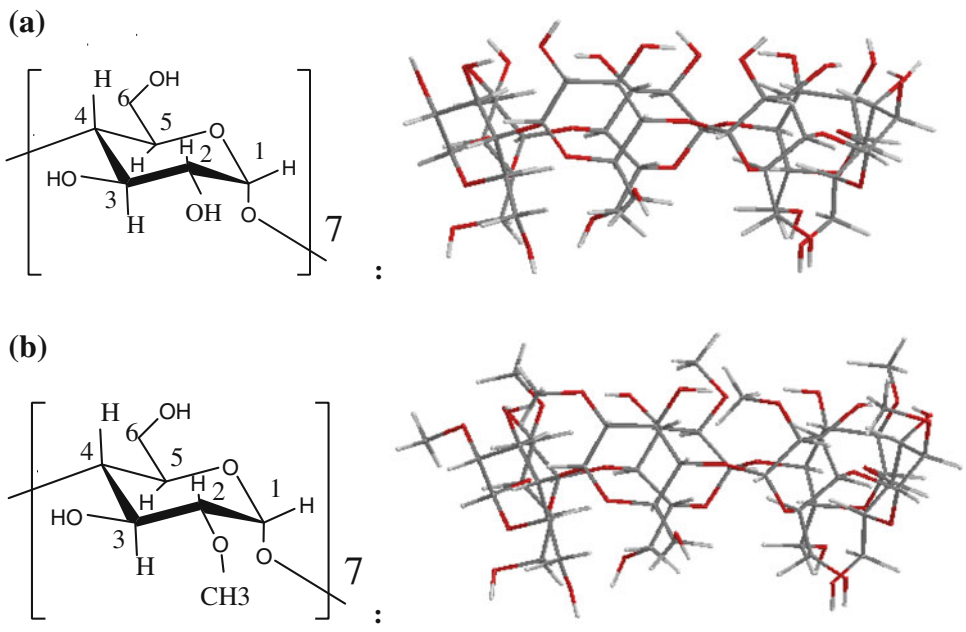

Fig. 1 **a** β-CD, **b** 2-Me-β-CD (Crysmeb)

doxycycline since it degrades under the influence of temperature, humidity and light. This complexation allows also to reduce irritation and to enhance the absorption rate [16].

The present study is related to a work on Crysmeb/doxycycline that was published in our previous preliminary communication [18]. We have theoretically studied this host–guest system using PM6 and ONIOM [B3LYP/6-31G(d):HF/3-21G*] methods. The complex formed with Doxycycline enol form has been found energetically more favorable. We found also various H-bonds, three conventional H-bonds and three weak H-bonds of type (C–H···O). In addition, one van der Waals interaction was observed between hydrogen atom H108 of Doxycycline and hydrogen atom H208 of cavity of Crysmeb [18].

In this work, three density functionals, M05-2X, B3LYP, B3PW91, were selected to generate ONIOM models in order to assessing their performance in the geometry optimizations of doxycycline:Crysmeb complex in the enol and keto forms. For this purpose, the geometries have been compared to that obtained with fully optimization at M052X/6-31G(d) level, which reproduces nicely the experimental structure. Herein, the 6-31G(d) basis set was applied to doxycycline, the most important part, and the 3-21G* basis set to cyclodextrin molecule which is considered as environment.

Computational method

The model of Crysmeb (Fig. 1a) was built by the Chem-Office package, starting from β-CD (Fig. 1b) at which seven methyl groups replacing hydroxyl hydrogen's have been attached at primary positions and is computed using the B3LYP density-functional treatment in the 3-21G* basis set (Fig. 1b).

The molecular structures of DOX in the keto and enol tautomeric forms were built by the Chem-Office package and were optimized using the density functional theory (DFT) method with B3LYP hybrid functional at the 6-31G* level (Fig. 2). The procedure of complexation was already described in our previous article [18]. All the calculations were carried out with the Gaussian 03 program [19]. In brief, the inclusion complexation was emulated by entering the guest molecule from the wide end of Crysmeb and then letting it pass through the Crysmeb in several steps. In each step, the geometry of the complex was fully optimized without any restriction using the PM6 method. This procedure of complexation was adapted for the keto and enol forms of doxycycline. DOX molecule was initially located at Z coordinates of -8 Å and was moved through the β-CD cavity along the Z axis to -2 Å with a stepwise of 0.5 Å. In order to find an even more stable structure of the complex, each DOX molecule was rotated around the C1–C2 bond of DOX that coincident with Z-axis, by 20° intervals from 0° to 360° (Figure. 3). Different minima were localized for the whole complex. The details of the optimization can also be found in former reports, the minimum energy for the enol form is located at -4 Å but for the keto form is located at -5 Å by PM6 method [18].

Hybrid energy methods such as ONIOM that combine different levels of theory into one calculation have been very successful in describing large systems [20–22]. The system was divided into two parts: the most important part, consisting of the guest molecule Doxycycline for the inner

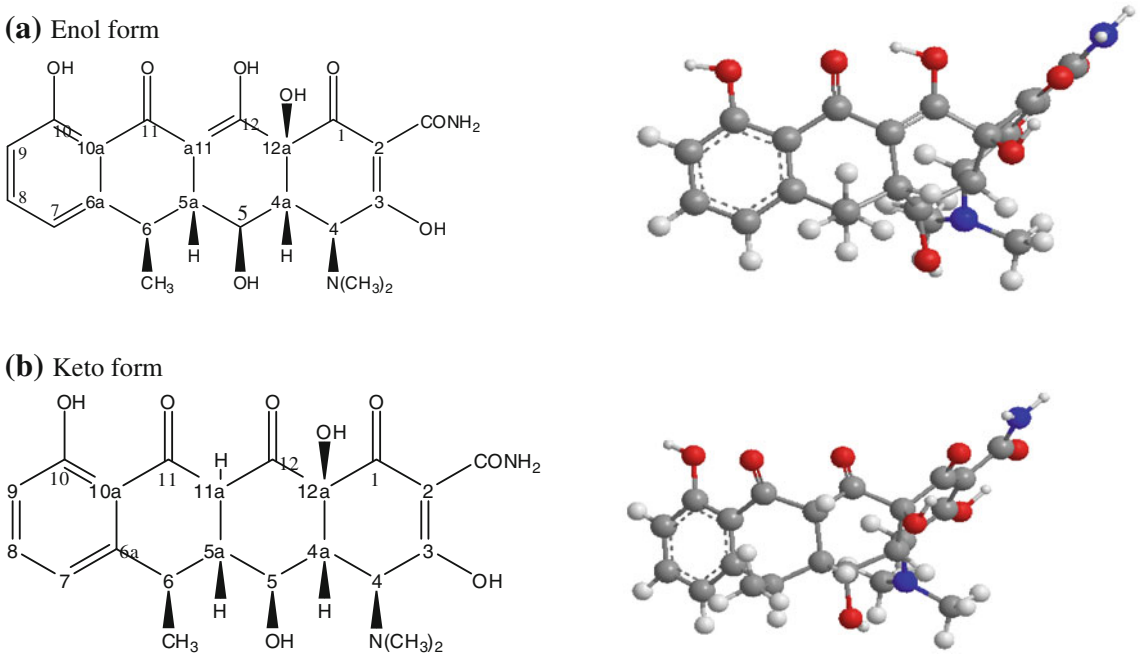

Fig. 2 Doxycycline optimized by B3LYP/6-31G(d)

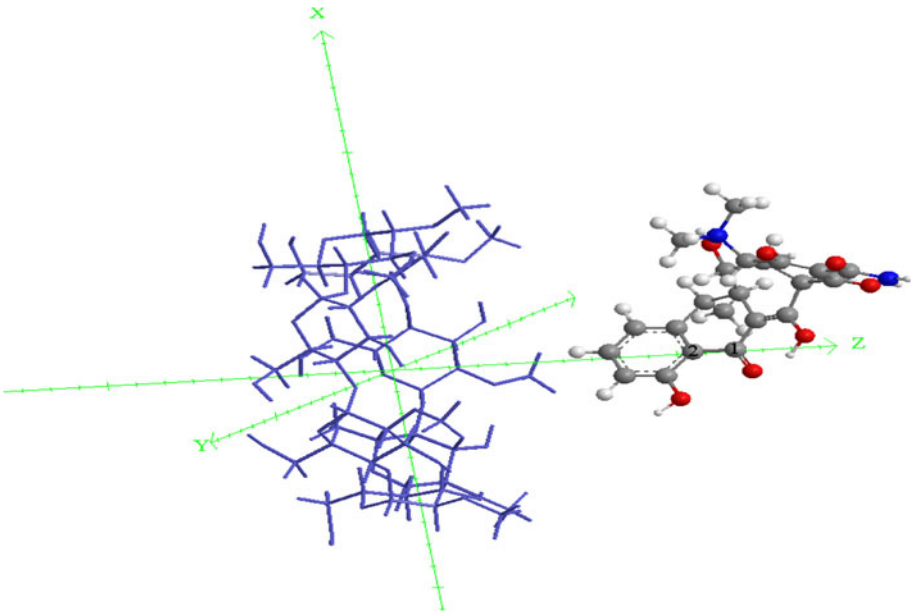

Fig. 3 The relative position between doxycycline and Crysmeb

layer; and the minor part, consisting of the remaining part Me-2-ß-CD (Crysmeb) for the outer layer. The integrated energy for the two-layered ONIOM approach is defined as:

$$E(ONIOM2) = E(high, model) + E(low, real) - E(low, model) \quad (1)$$

where $E(high, model)$ is the energy of the inner layer at the high level of theory (the doxycycline molecule), $E(low, real)$ 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 at the low level of theory (Me-ß-CD).

The complexation energy $E_{complexation}$ was defined as the difference between the sum of energy of individual host and guest molecule and the energy of inclusion complex is defined as the following formula:

Table 1 Complexation, binding and deformations energies (kcal/mol)

	Full DFT	ONIOM				B3LYP [6-31G(d): HF/3-21G*] [18]
	M052X/ 6-31G(d)	M052X [6-31G(d): 3-21G*]	B3LYP [6-31G(d): 3-21G*]	B3PW91 [6-31G(d): 3-21G*]	M052X [6-31G(d): HF/3-21G*]	
$E_{complexation}$ Complex (enol)	**−28.11**	−69.03	−43.54	−31.38	−22.59	−22.66
$E_{complexation}$ complex (keto)	**−26.35**	−55.85	−35.14	−21.33	−18.83	−17.52
$\Delta E_{complexation}$	**1.76**	13.18	8.40	10.05	3.76	5.14
$E_{binding}$ complex (enol)	**−43.93**	−104.60	−71.72	−62.12	−51.46	−51.06
$E_{binding}$ complex (keto)	**−37.02**	−80.95	−50.2	−37.02	−40.79	−31.65
$\Delta E_{binding}$	**6.91**	23.65	21.52	15.1	10.67	19.41
$E_{deformation}$*guest* complex (enol)	**1.88**	7.53	7.53	6.27	6.27	6.13
$E_{deformation}$*guest* complex (keto)	**3.01**	4.82	6.28	5.02	6.28	3.74

$$E_{complexation} = E_{complex} - (E^{opt}(host) + E^{opt}(guest)) \quad (2)$$

$$E_{binding} = E_{complex} - \left(E_{sp}^{opt}(host) + E_{sp}^{opt}(guest)\right). \quad (3)$$

Equal (4) stands for deformation energy of the component.

$$E_{deformation}(compoment) = E_{sp}^{opt}(compoment) - E_{opt}(compoment) \quad (4)$$

$E_{sp}^{opt}(compoment)$, is the single point energy of the component on the configuration taken from the optimized complex geometry, and $E_{opt}(compoment)$ is the energy of the optimized geometry of the free component.

The B3LYP [23–31] and B3PW91 [32–36] density functionals were employed as they are the most widely used density functional and the most popular. Also, we involve the Minnesota density M05-2X functional, a member of the M05 families of density functionals developed by Zhao, Truhlar and Schultz, which gave good accuracy for match problems [37, 38] and is beginning to be increasingly used [39–41] and which give us a good result in our study of the doxycycline:2-O-Methyl-βCD complex.

Finally, in the NBO approach, a stabilization energy E(2) related to the delocalization trend of electrons from donor to acceptor orbital is calculated via perturbation theory. A large stabilization energy E(2) between a Ione pair LP(Y) of one atom, and an antibonding σ^* (X–H) orbital, is generally indicative of a X–H···Y hydrogen bond [42, 43].

Results and discussion

The following table (Table 1) shows the complexation, binding and deformation energies of the inclusion complexes obtained with full DFT M05-2X/6-31G(d) and several ONIOM2 methods in the enol and keto forms. According to the results obtained in Table 1 we can see that with all methods used in this study, the enol form is given more favorable than the keto form relative to complexation or binding energies. Thus, the complexation energy difference between the two forms being equal to 1.76 kcal/mol at the target method M05-2X/6-31G(d). Regarding the ONIOM2 methods we can point out that both combinations, ONIOM2 (M05-2X/6-31G(d):HF/3-21G*) and ONIOM2 (B3LYP/6-31G(d):HF/3-21G*), gives relatively acceptable values relative to target value, being equal respectively to 3.76 and 5.14 kcal/mol; however, the three other combinations, ONIOM2 (M05-2X/6-31G(d):M05-2X/3-21G*), ONIOM2 (B3LYP/6-31G(d):B3LYP/3-21G*) and ONIOM2 (B3PW91/6-31G(d):B3PW91/3-21G*) perform badly and overestimates the values of complexation energies difference, being equal respectively to 13.18, 8.40 and 10.05 kcal/mol.

The calculated binding energies summarized in Table 1 indicates that with the target method DFT M05-2X/6-31G(d) is estimated equal to –43.93 kcal/mol for the enol form and equal to −37.02 kcal/mol for the keto form which means that enol form is more favorable than the keto one with 6.91 kcal/mol. The enol form is also given more favorable than the keto one with all ONIOM2 methods but with more or less different energetic values. Also, from Table 1, we can see that the not mixed combination ONIOM2 (M05-2X/6-31G(d):M05-2X/3-21G*) and ONIOM2 (B3LYP/6-31G(d):B3LYP/3-21G*) methods gave relatively poor results. Whereas, the mixed combination ONIOM2 (M05-2X/6-31G(d):HF/3-21G*) and ONIOM2 (B3LYP/6-31G(d):HF/3-21G*) offers relatively for the enol form the closest values of binding energies to that obtained with the target method. Surprisingly, the not mixed combination ONIOM2 (B3PW91/6-31G(d):B3PW91/3-21G*) reproduces exactly the binding energy of the keto form with the same energetic value.

So, considering binding energy we can roughly conclude that mixed combination ONIOM2 (M05-2X/6-31G(d):HF/3-21G*) offers relatively the closest value to the target

value with binding energies differences which is equal to 10.67 kcal/mol.

The computed deformation energies with DFT M05-2X/6-31G(d) (Table 1) indicate that doxycycline molecules needs only around 1.88 kcal/mol to conformational adaptation inside the cavity of Crysmeb for the enol form, and ca. 3.01 kcal/mol for the keto form. Unfortunately, all the deformation energies were overestimated with all the ONIOM2 method except the mixed combination ONIOM2 (B3LYP/6-31G(d):HF/3-21G*) method which predict deformation energy of the guest molecule in the keto form equal to 3.74 kcal/mol close to 3.01 kcal/mol of the target value.

The structures with minimum energy obtained from DFT M05-2X/6-31G(d) for the enol and keto forms of Doxycycline are shown in Fig. 4. Doxycycline tends to bond strongly with Crysmeb by penetrating its cavity by the wider and the more accessible face. However, the cavity of Crysmeb is just wide enough to allow full penetration for enol and keto forms of Doxycycline. Moreover, the Doxycycline molecule is too large to fit entirely in the cavity of Crysmeb and the effect of the steric barrier becomes large after natural β-CD was modified. As it was expected, the geometry of the Doxycycline:Crysmeb complex does not differ from that obtained with ONIOM2 (B3LYP/6-31G(d):HF/3-21G*) and Doxycycline fragment retains practically the same region of space [18]. In fact, an inspection of the geometry of the two complexes shows that the aromatic ring of doxycycline entered fully into the cavity of Crysmeb, while the methyl-6 group remains on the rim of Crysmeb on the one hand and the rest of the molecule keep outside the hydrophilic exterior of the cavity on the other hand. This obvious configuration is due certainly to the presence of CO, CONH2 and N(CH3)3 groups which add charged sites on the Doxycycline and make it more hydrophilic.

As regards the geometries (Fig. 5) obtained with all ONIOM2 methods we can say that the mixed combinations ONIOM2 (M05-2X/6-31G(d):HF/3-21G*) and ONIOM2 (B3LYP/6-31G(d):HF/3-21G*) reproduces nearly the target geometry structure. However, with not mixed

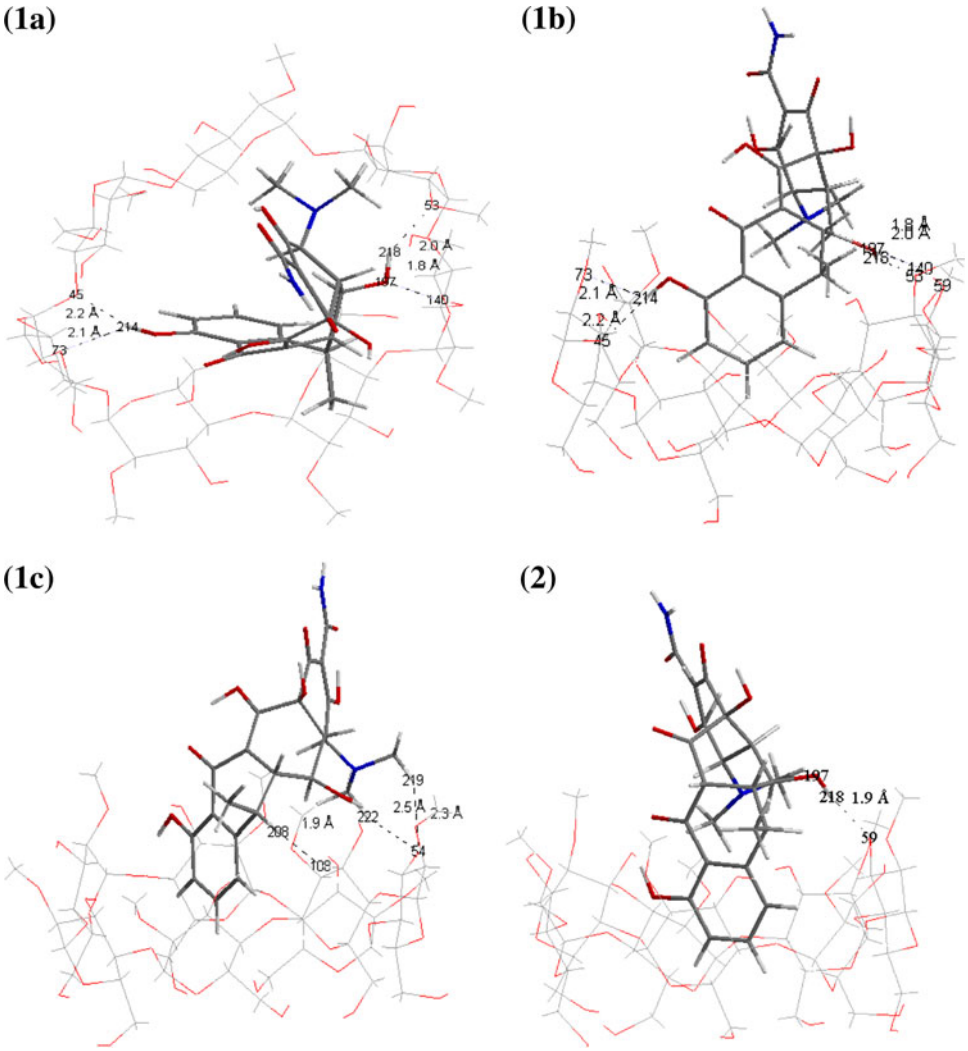

Fig. 4 Complex (enol form) optimized by M052X/6-31 g(d): **a** conventional H-bond O···HO from the top of the large rim of the Crysmeb, **b** from the sides of the Crysmeb wall, **c** weak and van der waals H-bond (O···HC and CH···CH) **2** keto form

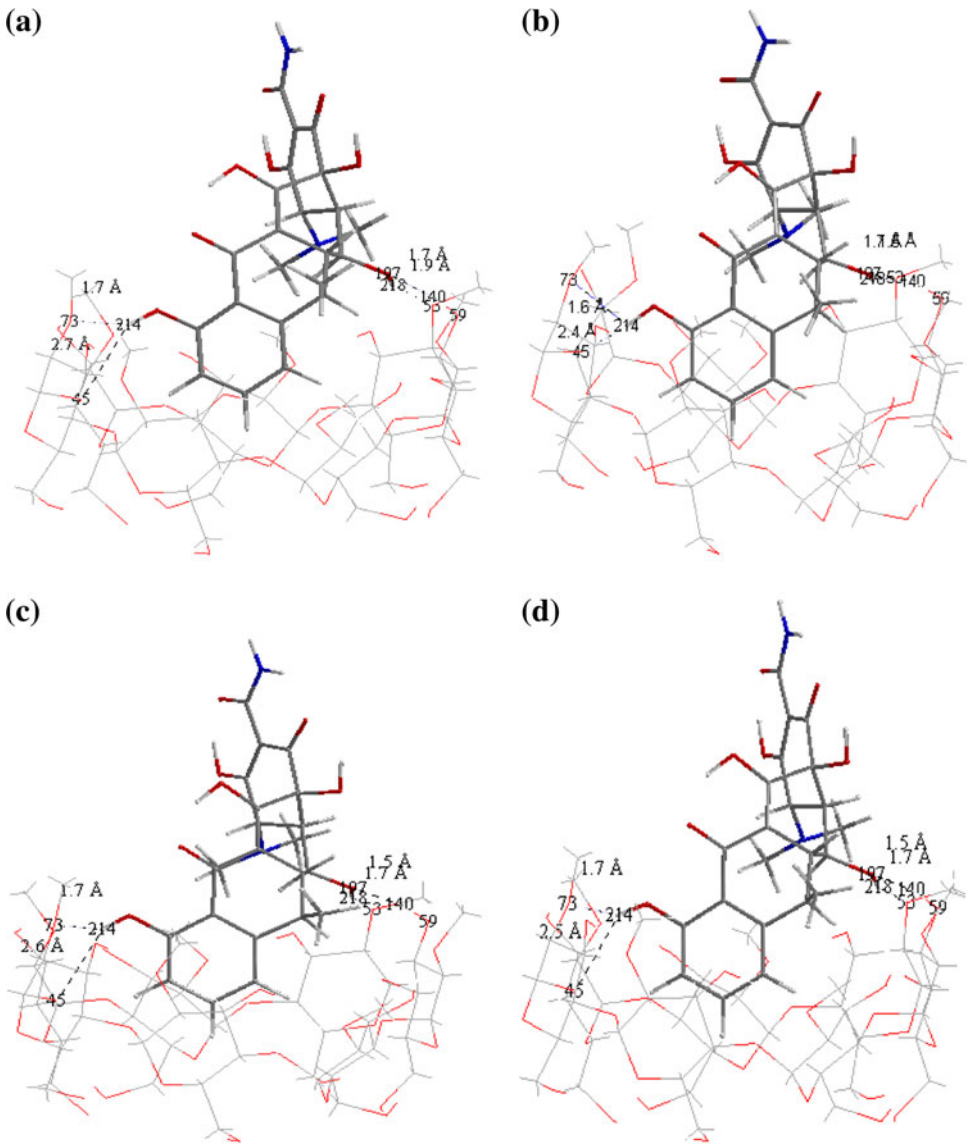

Fig. 5 Geometry of enol complex optimized by: **a** M05-2X(6-31G(d)/HF(3-21 g*), **b** M05-2X: (6-31G(d)/M05-2X: (3-21 g*), **c** B3PW91: (6-31G(d)/B3PW91: (3-21 g*), **d** B3LYP: (6-31G(d)/B3LYP: (3-21 g*)

combinations ONIOM2 methods, they reproduce correctly the inside of the cavity but some deformations of the doxycycline structure are observed outside the cavity relative to the target geometry structure.

In the NBO analysis of X–H···Y hydrogen bonded system, the interaction between the LP(Y) Ione pair of the proton acceptor and σ^*(X–H) anti-bond of proton donor is characterized by a significant E(2) stabilization energy. The later values are given in Table 2 in the enol form with full DFT and ONIOM2 methods.

Indeed, as it can be seen significant interaction energies are obtained for the expected hydrogen bonds (obtained with ONIOM2 (B3LYP/6-31G(d):HF/3-21G*)) except the H-bond with oxygen atom O45 which establish hydrogen bonding with hydrogen atom H214 (instead of H205) of H214–O195 separated by 2.1 Å with an O45···H214–O195 angle equal to 164.8°. The interaction of this energy H-bond is 5.87 kcal/mol (instead of 1.76 kcal/mol with ONIOM2 (B3LYP/6-31G(d):HF/3-21G*)).

Also, we observe three other conventional H-bond between respectively, oxygen atom O53 and hydrogen atom H218 of O197–H218 bond (2.0 Å, 147.3°), oxygen atom O73 and hydrogen atom H214 of H214–O194 bond (2.2 Å, 114.3°) and oxygen atom O197 and hydrogen atom H140 of H140–O59 bond (1.8 Å, 163.8°). The interaction energies of these hydrogen bonds are respectively, 6.67, 3.34 and 2.0 kcal/mol. These conventional H-bonds are assisted by two weak hydrogen bonds. The first one is established between oxygen atom O54 and hydrogen atom H219 of C199–H219 bond (2.3 Å, 146.8°) and the second one is established between oxygen atom O54 and hydrogen atom H222 of C200–H222 bond (2.5 Å, 142.7°). Their interaction energies are respectively equal to 2.05 and 1.65 kcal/mol.

Table 2 The electron donor and accepter orbital, the corresponding E(2) hydrogen bonds interactions energies, distances and angles obtained for enol complex

NBO donor	NBO acceptor	ONIOM				Full DFT
		M05-2x: 6-31g(d)/ HF: 3-21g*	M05-2x: 6-31g(d)/ M05-2x: −3-21g*	b3lyp: 6-31g(d)/ HF: 3-21g* [18]	b3lyp: 6-31g(d)/ b3lyp: 3-21g*	b3pw91: 6-31g(d)/ b3pw91: 3-21g*	M05-2x: 6-31g(d)
LP(1) O53	BD*O197-H218	9.48 (1.9 Å, 151.3°)	3.34 (1.7 Å,159.1°)	5.72 (1.8 Å, 153.8°)	3.95 (1.7 Å, 159.7°)	4.22 (1.7 Å, 159.9°)	6.67 (2.0 Å, 147.3°)
LP(1) O45	BD*O195-H214	0.97 (2.6 Å, 136.3°)	10.09 (1.6 Å, 171.1°)	0.69 (2.5 Å, 151.6°)	2.72 (2.5 Å, 132.6°)	0.62 (2.6 Å, 137,0°)	5.87 (2.1 Å, 164.8°)
LP(1) O45	BD*C177-H205	1.67 (2.5 Å, 150.2°)	0.41 (2.7 Å, 138,0°)	1.76 (2.5 Å, 151.6°)	3.95 (2.3 Å, 149.6°)	4.11 (2.2 Å, 155.4°)	0,85 (2.7 Å, 123.5°)
LP(2) O73	BD*O195-H214	0.89 (1.7 Å, 150.1°)	1.15 (2.4 Å, 101.1°)	1.32 (1.5 Å, 150.0°)	0.16 (1.7 Å, 149.8°)	0.57 (1.7 Å, 149.1°)	3.34 (2.2 Å, 114.3°)
LP(1) O54	BD*C199-H219	2.83 (2.2 Å, 146.3°)	6.47 (2.1 Å, 147.7°)	1.96 (2.2 Å, 151.7°)	4.34 (2.1 Å, 152.4°)	3.70 (2.1 Å, 151.8°)	2.05 (2.3 Å, 146.8°)
LP(1) O54	BD*C200-H222	1.96 (2.2 Å, 152.0°)	3.35 (2.3 Å, 142.1°)	1.70 (2.4 Å, 145.3°)	1.38 (2.4 Å, 141.9°)	1.62 (2.4 Å, 142.6°)	1.65 (2.5 Å, 142.7°)
LP O197	BD*O59-H140	1.63 (1.6 Å, 169.3°)	2.69 (1.5 Å, 157.8°)	2.32 (1.7 Å, 169.7°)	0.80 (1.5 Å, 164.4°)	1.13 (1.5 Å, 165.8°)	2.00 (1.8 Å, 163.8°)
BD C21-H108	BD*C183-H208	0.97 (1.9 Å, 159.8°)	1.23 (1.9 Å, 154.9°)	1.37 (1.9 Å, 170°)	1.4 (1.7 Å, 162.5°)	2.48 (1.7 Å, 162.1°)	1.47 (1.9 Å, 172.0°)

NBO calculation confirms also in all ONIOM methods and full DFT(M05-2X), the existence of a Van der Waals interaction detected by RMN only in the enol form [16], between the donor C21–H108 of Doxycycline and the accepter C183–H208 of Crysmeb. The distance of H-bond is 1.9 Å (1.47 kcal/mol) and and almost linear angle 172° (full DFT).

Intramolecular hydrogen bonding (Table 3 and 4) can be also a significant factor in determining the preference in Doxycycline:Crysmeb complex. First of all, it is important to know that several intramolecular H-bonds can occur in Doxycycline molecule and its inclusion in the CD cavity can allow their disappearance or may be the appearance of the new one.

Both of the enol and the keto forms the same intramolecular hydrogen bonding was observed in the doxycycline molecule except with oxygen atom O193 which establish differently intramolecular hydrogen bonding. The first one, it is established with hydrogen atom H213 of H213–O194 bond in the enol form, however, in the keto form the hydrogen bond was observed with hydrogen atom H214 of H214–O182 bond.

Thus, for the oxygen atom O192 and in both forms, enol and keto, it was established two hydrogen bond, the first one is predict with hydrogen atom H212 of the H212–0191 bond. This interaction is estimated equal to 5.73 kcal/mol using full M05-2X\6-31G(d). The estimation of this interaction using ONIOM2 methods gives to ONIOM2 (M05-2X 6-31G(d):HF 3-21G*) the best result, with an estimation equal to 5.89 kcal/mol. The second one, is established with hydrogen atom H204 of the N176–H204 bond, this interaction was estimated equal to 6.80 kcal/mol using full M05-2X\6-31G(d). ONIOM2 (M05-2X 6-31G(d):HF 3-21G*) gives the best evaluation to the target method which stabilization energy E(2) was estimated equal to 6.86 kcal/mol.

Thus, for the oxygen atom O175 and in both forms, enol and keto, it was established one intramolecular hydrogen bond with hydrogen atom H202 of the O173–H202 bond. This interaction was estimated equal to 10.06 and 10.01 kcal/mol respectively for the enol and keto forms using ONIOM2 (M05-2X 6-31G(d):HF 3-21G*). Among the ONIOM2 methods used for estimating these interactions, the ONIOM2 (M05-2X 6-31G(d):HF 3-21G*) gives for both forms the best result with estimating this interaction equal to 9.92 for the enol and keto forms.

It is important to notice that this previous interaction has been overestimated with all the methods.

Finally, for the oxygen atom O193, it bond differently in both forms. Thus, in the enol form case, is establishing hydrogen bond with hydrogen atom H213 of the O194–H213 bond. This interaction was estimated equal to 6.06 kcal/mol using full M05-2X (6-31G(d)). Therefore,

Table 3 Intramolecular hydrogen bond in free doxycycline (enol) and in the inclusion complexes

Doxycycline (enol)		M0-52X: (6-31g(d))	M05-2x: 6-31g(d)/ M05-2X: 3-21 g*	M05-2x: 6-31g(d)/ HF: 3-21g*		b3pw91: 6-31g(d)/ b3pw91: 3-21g*		b3lyp: 6-31g(d)/ b3lyp: 3-21g*	b3lyp: 6-31g(d)/ HF: 3-21g* [18]	
NBO donor	NBO acceptor	Inclusion-complex	Inclusion-complex	Inclusion-complex	Free	Inclusion-complex	Free	Inclusion-complex	Inclusion-complex	Free
LP O192	BD*O191-H212	5.73 (1.95 Å)	8.57 (1.95 Å)	6.04 (1.94 Å)	4.58 (2.00)	5.06 (1.9 Å)	4.52 (1.98 Å)	7.27 (1.93 Å)	5.89 (1.9 Å)	7.21 (2.0 Å)
LP O192	BD*N176-H204	6.80 (1.93 Å)	9.53 (1.93 Å)	6.86 (1.92 Å	7.16 (1.92 Å)	7.27 (1.93 Å)	8.10 (1.88 Å)	5.96 (1.9 Å)	7.37 (1.9 Å)	7.73 (1.9 Å)
LP O175	BD*O173-H202	10.05 (1.41 Å)	12.45 (1.42 Å)	9.92 (1.42 Å)	10.10 (1.39 Å)	9.45 (1.46 Å)	9.70 (1.44 Å)	9.00 (1.5 Å)	8.95 (1.5 Å)	9.20 (1.5 Å)
LP O193	BD*O194-H213	6.06 (1.7 Å)	7.65 (1.67 Å)	6.16 (1.67 Å)	6.70 (1.64 Å)	5.72 (1.63 Å)	6.86 (1.57 Å)	5.72 (1.6 Å)	5.57 (1.6 Å)	6.32 (1.6 Å)

Table 4 Intramolecular hydrogen bond in free doxycycline (keto) and in the inclusion complexes

Doxycycline (keto)		M0-52X: (6-31g(d))	M05-2x: 6-31g(d)/ M05-2X: 3-21g*	M05-2x: 6-31g(d)/ HF: 3-21g*		b3pw91: 6-31g(d)/ b3pw91: 3-21g*		b3lyp: 6-31g(d)/ b3lyp: 3-21g*	b3lyp: 6-31g(d)/ HF: 3-21g* [18]	
NBO donor	NBO acceptor	Inclusion-complex	Inclusion-complex	Inclusion-complex	Free	Inclusion-complex	Free	Inclusion-complex	Inclusion-complex	Free
LP O192	BD*O191-H212	6.34 (1.94 Å)	9.55 (1.92 Å)	6.37 (1.94 Å)	5.86 (1.96 Å)	9.40 (1.89 Å)	10.92 (1.93 Å)	6.51 (1.92 Å)	6.44 (1.9 Å)	3.98 (2.01 Å)
LP O192	BD*N176-H204	6.71 (1.93 Å)	9.88 (1.93 Å)	6.78 (1.93 Å)	6.51 (1.93 Å)	9.76 (1.9 Å)	5.14 (1.90 Å)	7.02 (1.91Å)	7.14 (1.9 Å)	7.86 (1.9 Å)
LP O175	BD*O173-H202	10.01 (1.41 Å)	12.73 (1.39 Å)	9.92 (1.41 Å)	9.49 (1.41 Å)	9.40 (1.5 Å)	10.78 (1.45 Å)	6.51 (1.5 Å)	8.84 (1.5 Å)	9.35 (1.5 Å)
LP O193	BD*O182-H214	6.25 (1.7 Å)	5.02 (1.83 Å)	6.61 (1.67 Å)	x	6.47 (1.68 Å)	x	4.80 (1.75 Å)	5.13 (1.7 Å)	x

ONIOM2 (M05-2X 6-31G(d):HF 3-21G*) gives the closest result to the target method in estimating this interaction equal to 6.16 kcal/mol. And the other hand, in the keto case, the hydrogen bond was observed only upon complexation with this oxygen atom O193 hydrogen atom H214 of the O182-H214 bond. This interaction is predicting equal to 6.25 kcal/mol with the target method. The ONIOM2 (M05-2X 6-31G(d):HF 3-21G*) gives the best estimation among the ONIOM2 methods with an estimating the stabilization energy E(2) equal to 6.61 kcal/mol.

Conclusion

This comparative study of some ONIOM2 methods applied to study the stability of Doxycycline: Crysmeb inclusion complex compared to the target method (full M05:6-31G(d)). The results obtained with all ONIOM2 methods give quantitatively same conclusions to that obtained with the target method. However the mixed ONIOM2 method which combine DFT and HF methods give much best results to the not mixed method which use only DFT method in the two layers. Thus, we have shown that both ONIOM2 (M05-2X 6-31G(d):HF 3-21G*) and ONIOM2 (B3LYP 6-31G(d):HF 3-21G*) give relatively accurate predictions to complexation, binding and deformation energies for this complex. Moreover, these ONIOM2 methods reproduces roughly the geometry to that obtained with the target method end gives almost the estimated values of the inter and intra hydrogen bonds.

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References

1. Szejtli, J.: Chem. Rev. **98**, 1743 (1998)
2. Connors, K.A.: Chem. Rev. **97**, 1325 (1997)
3. Martin Del Valle, E.M.: Process Biochem. **39**, 1033 (2004)
4. Salem, L.B., Bosquillon, C., Dailey, L.A., Delattre, L., Martin, G.P., Evrard, B., Forbes, B.: J. Controlled Release **136**, 110–116 (2009)
5. Szejtli, J., Cyclodextrine and their inclusion complex. vol. 10, p.159. Akadémiai kiado, Budapest (1981)
6. Maestrelli, F., Cecchi, M., Cirri, M., Capasso, G., Mennimi, N., Mura, P.: J. Incl. Phenom. Macrocycl. Chem. **66**, 18–25 (2009)
7. Viernstein, H., Weiss-Greiler, P., Wolschann, P.: J. Incl. Phenom. Macrocycl. Chem. **44**, 235–239 (2002)
8. Cao, Y., Xiao, X., Lu, R., Guo, Q.: J. Inclu. Phenom. Macrocycl. Chem. **46**, 195–200 (2003)
9. Luo, X., Chen, Y., Gastpard Huber, J., Zhang, Y., Sinay, P.: C.R. Chimie **7**, 25–28 (2004)
10. Hamai, S.: Bull. Chem. Soc. Jpn. **65**, 2323–2327 (1992)
11. Sweet, R.L., Schachter, J., Landers, D.V., Ohm-Smith, M., Robbie, M.O.: Am. J. Obstet. Gynecol. **158**(3 Pt 2), 736–741 (1988). PMID 3162653
12. Gjønnaess, H., Holten, E.: Acta Obstet. Gynecol. Scand. **57**(2), 137–139 (1978). doi:10.3109/00016347809155893. PMID 345730
13. Määttä, M., Kari, O., Tervahartiala, T., et al.: Graefes Arch. Clin. Exp. Ophthalmol. **244**(8), 957–962 (2006). doi:10.1007/s00417-005-0212-3. s 16411105
14. Quarterman, M.J., Johnson, DW, Abele, D.C., Lesher, J.L., Hull, D.S., Davis, L.S.: Arch Dermatol **133**(1), 454(1997). doi:10.1001/archderm.133.1.49. PMID 9006372
15. International Journal of Pharma and Bio Sciences V1(2)2010
16. Bakkour, Y., Vermeersch, G., Morcelet, M., Boschin, F., Martel, B., Azaroual, N.: J. Incl. Phenom. Macrocycl. Chem. **54**, 109 (2006)
17. Bakkour, Y.: Thesis, Lile 1 (2005)
18. Benghodbane, S., Khatmi, D.: A theoretical study on the inclusion complexation of doxycycline with Crysmeb. C. R. Chimie (2011), doi:10.1016/j.crci.2011.11.007
19. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Montgomery, J.A. Jr., Vreven, T., Kudin, K.N., Burant, J.C., Millam, J.M., Iyengar, S.S., Tomasi, J., Barone, V., Mennucci, B., Cossi, M., Scalmani, G., Rega, N., Petersson, G.A., Nakatsuji, H., Hada, M., Ehara, M., Toyota, K., Fukuda, R., Hasegawa, J., Ishida, M., Nakajima, T., Honda, Y., Kitao, O., Nakai, H., Klene, M., Li, X., Knox, J.E., Hratchian, H.P., Cross, J.B., Adamo, C.,Jaramillo, J., Gomperts, R., Stratmann, R.E., Yazyev, O., Austin, A.J., Cammi, R., Pomelli, C., Ochterski, J.W., Ayala, P.Y., Morokuma, K., Voth, G.A., Salvador, P., Dannenberg, J.J., Zakrzewski, V.G., Dapprich, S., Daniels, A.D., Strain, M.C., Farkas, O., Malick, D.K., Rabuck, A.D., Raghavachari K, Foresman, J.B., Ortiz, J.V., Cui, Q., Baboul, A.G., Clifford, S., Cioslowski, J., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Challacombe, M., Gill, P.M.W., Johnson, B., Chen, W., M. Wong, M.W., Gonzalez, C., Pople, J.A.: Gaussian 03, Revision E.01. Gaussian Inc., Pittsburgh, PA (2009)
20. Maseras, F., Morokuma, K.: J. Comput. Chem. **16**, 1170 (1995)
21. Dapprich, S., Komáromi, I., Byun, K.S., Morokuma, K., Frisch, M.J.: J. Mol. Struct. TheoChem. **1**, 461–462 (1999)
22. Tschumper, G.S., Morokuma, K.: J. Mol. Struct. TheoChem. **592**, 137–147 (2002)
23. Xia, Y., Wang, X., Zhang, Y., Luo, B.: Comput. Theor. Chem. (2011). doi:10.1016/j.copmtc.2011.03.010
24. Stewart, J.J.P.: J. Mol. Model. **14**, 499–535 (2008). doi:10.1007/s00894-008-0299-7
25. Stewart, J.J.P.: J Mol Model. **13**, 1173–1213 (2007)
26. Giussi, J.M., Gastaca, B., Albesa, A., Cortizo, M.S., Allegretti, P.E.: Spectrochim. Acta A **78L**, 868–873 (2011)
27. Morokuma, K.: Bull. Korean Chem. Soc. **24**(6), 797–801 (2003)
28. Snor, W., Liedl, E., Weiss-Greiler, P., Viernstein, H., Wolschann, P.: Int. J. Pharm. **381**, 146–152 (2009)
29. Huang, M.-J., Quan, Z., Liu, Y.M.: Int J Quantum Chem. **109**(1), 81–90 (2009). doi:10.1002/qua.21852
30. Becke, A.D.: J. Chem. Phys. **37**, 5648–5652 (1993)
31. Li, W., Bitai, L., Chen, F., Yang, F., Wang, Z.: J. Mol. Struct. **990**, 244–252 (2011)
32. Ramalingama, S., Periandy, S.: Spectrochim. Acta A **78**, 1149–1161 (2011)
33. Liu, L., Gao, H.: Spectrochim. Acta A. **89**, 201–209 (2012)
34. Willis, B.G., Jensen, K.F.: J. Phys. Chem. A **102**, 2613–2623 (1998)
35. Sadjadi, M.S., Sadeghi, B., Zare, K.: THEOCHEM **817**, 27–33 (2007)

36. Jalbout, A.F., Nazari, F., Turker, L.: Volume. J. de la struct. mol. (Theochem) **671**(13), 1–21 (2004)
37. Helios, K., Wysokiński, R., Pietraszko, A., Michalska, D.: Vib. Spectrosc. **55**, 207–215 (2011)
38. Gu, J., Wang, J., Leszczynski, J.: Chem. Phys. Lett. **512**, 108–112 (2011)
39. Yan, L., Wenping, G., Weibin, F., Zhangfeng, Q., Jianguo, W.: Chin. J. Catal. **31**, 12 (2010)
40. Zhao, Y., Schultz, N.E., Truhlar, D.G.: J. Chem. Theory Comput. **2**, 364 (2006)
41. Zhao, Y., Truhlar, D.G.: J. Chem. Theory Comput. **3**, 289 (2007)
42. Bocca, C.C., Pontes, R.M., Basso, E.A.: J. Mol. Struct. (Theochem) **710**, 105–110 (2004)
43. Sosa, G.L., Peruchena, N.M., Contreras, R.H., Castro, E.A.: J. Mol. Struct. (Theochem) **577**, 219–228 (2002)