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Theoretical Investigation of the Complexation Reaction of Procaine-hydrochloride by β-cyclodextrin

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Quantum-chemical calculations were performed to study the complexation of drug molecule procaine hydrochloride with beta cyclodextrin (β-CD) in the gas phase and in water. The inclusion process was optimized by the semi empirical method PM3 and the obtained complex structure was further refined by ONIOM method (DFT:PM3). It was found that B3LYP/6-31G(d,p):PM3 provides the best energy minimum for the complex compared to M06-2X and WB97XD functionals. Given the energy profile, the configuration of the complex formed indicates that the benzene ring is completely included in the hydrophobic cavity of β-CD. The thermodynamic parameters analysis has shown that the procaine/β-CD complexation is enthalpically favorable, and the complex is well structured. Natural bond orbital (NBO) analysis indicates that no hydrogen bond interaction exists, and the procaine/β-CD complex is mainly stabilized by Van der Waals forces. The 1D ^{1}H NMR spectral analysis shows that the procaine molecule penetrates into the cavity of this CD with the aromatic ring.

Keywords: Host-guest inclusion, Procaine, β-cyclodextrin, PM3, ^{1}H NMR, NBO

INTRODUCTION

Most bioactive substances are hydrophobic molecules with weak chemical stability and many side effects [1-4]. Their direct administration through oral route is often impractical, and thus they must be formulated as a molecular complex with different other compounds named excipients or carriers. Amongst the different available excipients, cyclodextrins (CD's) represent the most feasible choice because they are natural non-toxic biodegradable molecules able to protect and to carry many hydrophobic molecules [5]. Precisely, CDs are cyclic molecules constituted by D-glucopyranosyl units bound by α-1,4 glucosidic bonds (Fig. 1a) forming a torus-like structure with hydrophilic faces bearing hydroxyl moieties and a hydrophobic interior called cavity [6,7]. Thanks to these structural and chemical characteristics, CDs are generally better water soluble molecules and can incorporate into their cavities' molecules of appropriate size to form inclusion complexes (host-guest type complexes) of different stoichiometries (1:1, 1:2, 2,1…). The extensive experimental works are performed to optimize the stability of the CD complexes and to test the bioavailability and bioactivity of the bounded guest molecules [8-11]. However, experimental studies are not the only tool used to investigate the complexation reactions of such system but quantum modeling and simulation methods are employed to acquire information about the stability of the complex. Nowadays, quantum modeling is becoming an essential tool in all areas of physical chemistry studies and is often used to confront many complicated chemical problems difficult to address with conventional experimental methods or when spectral signals need more accurate identification. In fact, these methods provide valuable information about the complexation process such as stoichiometry, geometry of the complex, and many electronic and thermodynamic parameters [12-14].

In the field of supramolecular chemistry, computational

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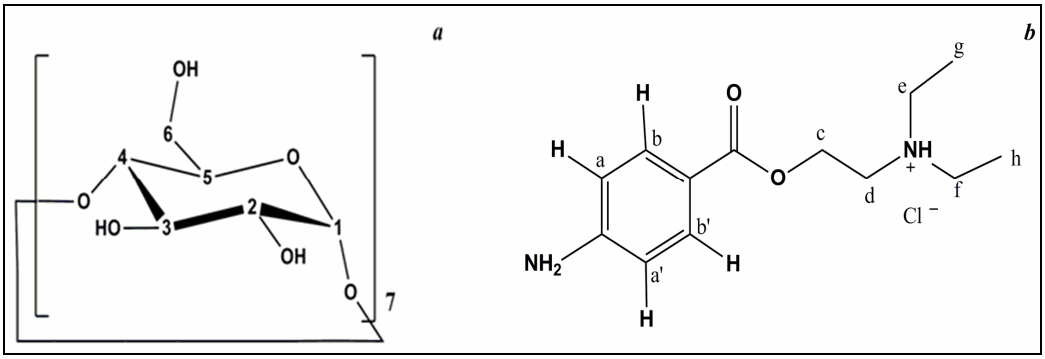

Fig. 1. Structures of β-CD (a) and procaine hydrochloride (b).

methods are performed to examine the complexation pathways of different fragments constituting the super molecule and to determine the most stable configuration. Although, these information are important, other ones more interesting are also addressed as the identification of the main interactions responsible for the stability amongst Van der Waals forces, charge transfer and hydrogen bonding.

In this study, quantum methods are used to study the complexation reaction of procaine hydrochloride with β-CD in vacuum and in water. The guest molecule (Fig. 1b) is a local anesthetic widely used in minor chirurgical surgery. However, its utilization is threatened by many adverse effects such as low aqueous solubility, tissue irritation and toxicity [4,15]. So, it is recommended to use it as a CD-complex to overcome these drawbacks.

Many theoretical works using *ab initio*, semi-empirical, and DFT methods are routinely conducted to characterize beta cyclodextrin (β-CD) inclusion complexes in gas and aqueous phases [12,14,16], however, only few ones studied the procaine cyclodextrin interaction. Thus, in this article, a potential energy surface (PES) is performed by PM3 method to examine the insertion pathway and to determine the configuration of the most stable inclusion complex of β-CD/Procaine. In the second step, DFT calculations are performed with different functionals using ONIOM method. The determination of the interactions involved is possible by analyzing the natural bond orbital (NBO). This method is efficient for studying intra and intermolecular bonding, and also provides a convenient basis for investigating charge transfer in molecular systems. Nuclear magnetic resonance spectroscopy (^{1}H NMR) is used as a characterization technique to also help us establish an approximate geometry of the complex.

Computational Methods

All calculations were performed with the Gaussian 09 software package [17]. The initial structure of procaine was constructed using the GaussView 3.0 software and that of β-CD was taken from Chem-office 3D ultra (version 6.0, Cambridge software). The two structures, procaine and β-CD, were firstly optimized separately by PM3 method [18] to get the starting optimized geometries needed for the scan. This semi-empirical method is preferred amongst others because it is recognized to be the most appropriate method in the conformational study of supra-molecular systems such as inclusion compounds; it offers better performance and gives good estimates for starting geometry optimization [19-22]. For all the starting structures, frequency calculations were carried out to confirm the completeness of optimization. For the insertion process of the guest molecule into the β-CD cavity, two orientations are possible; the amino fragment ($-NH_2$) of the procaine was oriented towards primary (orientation 1) or the secondary face (orientation 2) of the CD as shown in Fig. 2, and the insertion is performed until the detection of the minimum energy. The inclusion process was carried out along the Z axis with a pitch of 0.5 Å (Fig. 2). During the insertion process, β-CD atoms are kept frozen.

It is worth noting that the bulky quaternary $(-NH(C_2H_5)_2)^+$ group of procaine cannot be inserted into both CD faces because of the steric effects, which is consistent with the result found by Pirnau *et al*. using NMR

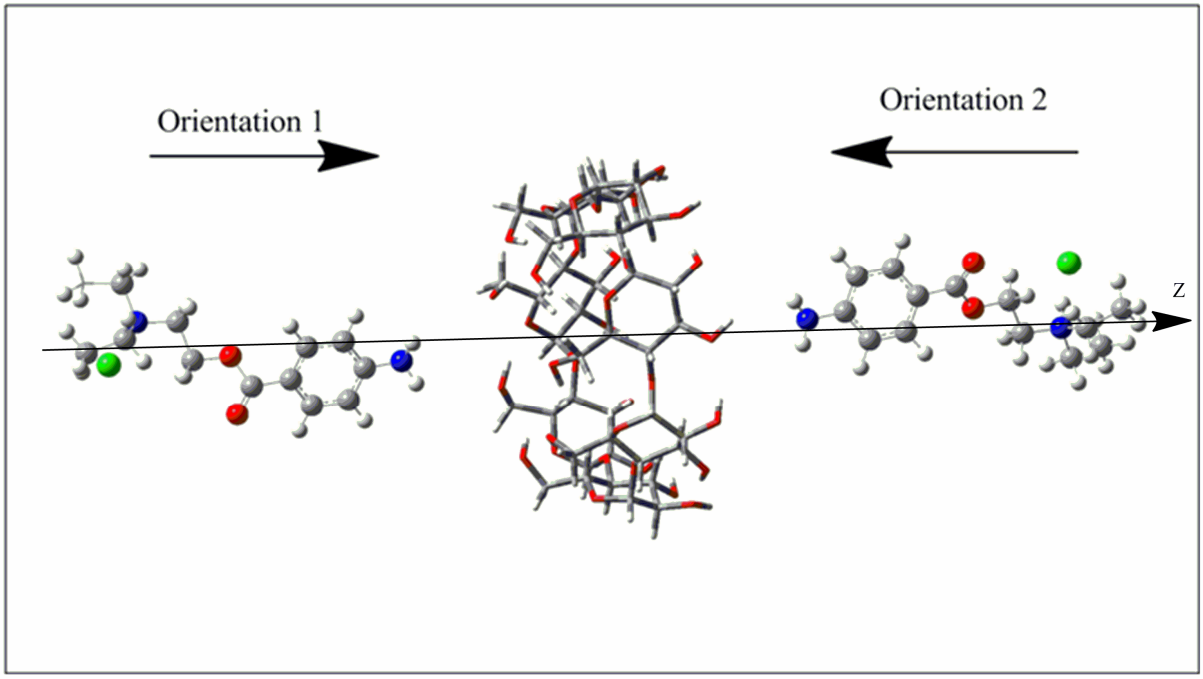

Fig. 2. Inclusion of procaine-hydrochloride into β-CD.

spectroscopy [9].

A further more accurate calculation was performed on the complex structure at the minimum by the ONIOM method [23]. In this method, two methods of quantum modeling are combined; a semi empirical method (PM3) and a more accurate one 'the density functional theory (DFT)'. The whole system (complex) is divided into two level systems, the model (procaine) and the real system (complex). A high level calculation (DFT) is performed for the model system, whereas a low level of the calculation (PM3) is performed for the model and the real systems.

$$E_{ONIOM} = E_{low}\,(Real) + E_{high}\,(Model) - E_{low}\,(Model) \quad (1)$$

Three exchange and correlation functional are chosen; B3LYP: the most used functional in the calculations of quantum chemistry because of its efficiency and the quality of the results, WB97XD: the scattering functional, used to study long-range interactions, and M06-2X: functional used to predict the presence of hydrogen bonds. The base of atomic orbitals used in ONIOM and NBO calculations is 6-31g(d,p).

The minimum energy is estimated in terms of the complexing energy and is given by the relation (Eq. (2)):

$$E_{complexation} = E_{complex} - (E^{opt}{}_{\beta\text{-}CD} + E^{opt}{}_{procaine}) \quad (2)$$

where $E_{complex}$, E^{opt} (β-CD) and E^{opt} (procaine) in Eq. (2), respectively denote the energies of the optimized geometries of the 1:1 complex, the free host molecule (β-CD) and the free guest molecule (procaine).

During the inclusion process, the guest molecule (procaine) will undergo a structural deformation resulting from its interaction with the host molecule. This strain energy is obtained by Eq. (3):

$$E_{deformation} = E\,(guest)^{opt}{}_{sp} - E(guest)^{opt} \quad (3)$$

where $E^{opt}{}_{sp}$ (guest) is the single point energy of the guest using its geometry in the optimized complex, and E^{opt} (guest) is the energy of the optimized geometry of the free guest.

The analysis of the nature of intermolecular interactions (host-guest) is done by using the natural bond orbital (NBO) method. The charge transfer between the occupied NBOs (donors) of Lewis type and unoccupied NBOs (acceptors) is

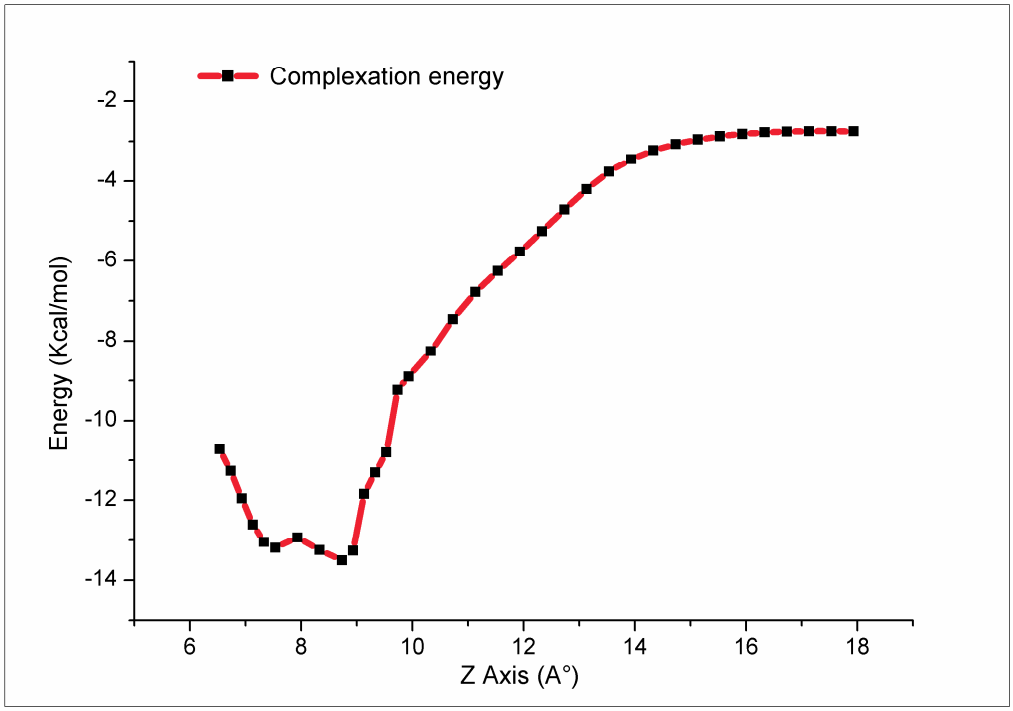

Fig. 3. Complexation energy of the procaine/β-CD complex at different positions.

estimated by the theory of second-order perturbation. For each NBO donor (i) and acceptor (j), the stabilization energy is given by Eq. (4) [24],

$$E^{(2)} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i} \quad (4)$$

where q_i is the occupation of the donor orbital, F (i, j) is the Fock operator and εi, εj are the energies of the NBOs orbitals.

The calculations of maximum UV-Vis absorption of procaine and the complex were performed by the TD-DFT method. The effect of complexation of procaine on the spectral information has been investigated using the PCM model for water as a solvent with B3LYP/6-31G(d,p) method.

RESULTS AND DISCUSSION

The complexation reaction is performed by considering the 1:1 stoichiometry. The SCAN calculations indicate that no minimum energy was observed during the insertion of the amino fragment (-NH_2) of procaine by the primary side of β-CD (orientation 1). Only the insertion of the procaine by the secondary side (orientation 2) led to a minimum of energy as shown in the curve of the energy potential obtained by the PM3 method (Fig. 3).

The negative values of the complexation energies for all the positions on the PES curve mean that the complex structure is more stable with respect to the starting structures. The complexation energy at the minimum (-13.5 kcal mol^{-1}), a rather weak value,suggests that procaine may be easily released when it arrives at the organism. Nevertheless, the real energetic minimum corresponds to the minimum of which the atoms of β-CD are not frozen, it is then necessary to release completely the structure of the complex to have the true minimum. The obtained energies under the free state in vacuum and in water are respectively -1577.2, -1603.07 kcal mol^{-1} and vibrational frequency calculation confirms that the structure of the complex corresponds effectively to a stationary state. From Fig. 4, the architecture of the inclusion complex at the minimum shows that the procaine benzyl ring penetrates

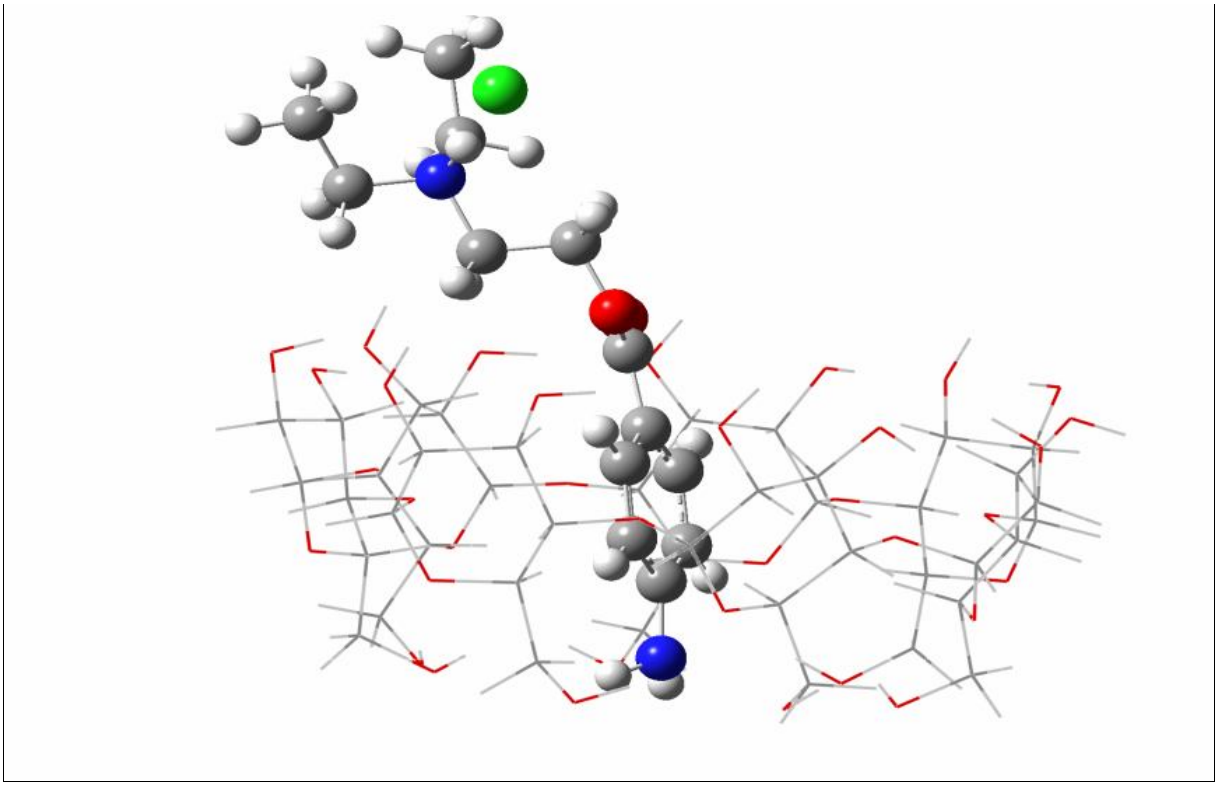

Fig. 4. Structure of the procaine/β-CD complex.

Table 1. The Main Energy Quantities of the Procaine/β-CD 1:1 Complex

	Complex	
	In vacuum	In water
Energy PM3 (kcal mol^{-1})	-1549.86	-1603.07
HOMO/LUMO gap (eV)	8.272	8.61
$\Delta_r G°$ (kcal mol^{-1})	-310.78	-319.55
Complexation energy (kcal mol^{-1})	-13.51	-14.68
Interaction energy (kcal mol^{-1})	-14.7	-14.94
Deformation energy of procaine (kcal mol^{-1})	1.2	1.27
Variation of entropy ΔS (cal/mol K^{-1})	-66.41	-67.04
ONIOM [B3LYP/6-31(d,p): PM3] (kcal mol^{-1})	772216.17	-
ONIOM [M06-2X/6-31(d,p): PM3] (kcal mol^{-1})	-771956.17	-
ONIOM [WB97XD/6-31(d,p): PM3] (kcal mol^{-1})	-772038.37	-

completely into the cavity of β-CD.

The portion of the guest molecule remaining outside the cavity may be surrounded by other β-CD molecules or more likely by solvent molecules because this part represents a hydrophilic pole. In order to obtain very accurate results for the complex geometry obtained, we carried out optimization calculations by the ONIOM method. The main energy quantities obtained are gathered in Table 1.

From Table 1, we can note that when the solvation effect is taken into consideration, the complexation energy and the HOMO/LUMO gap become respectively -14.68 kcal mol^{-1} and 8.61 eV, the solvent is than a factor favoring the complexation reaction. The structure of procaine was deformed due to the interaction forces exerted on it by β-CD without destruction of any covalent bond. The thermodynamic data obtained after vibration frequency calculations indicate that the complex formed is well structured (variation of the entropy is negative) and the complexation reaction is favored thermodynamically ($\Delta_r G < 0$). On the other hand, using the ONIOM method allows selecting the best combination between two computational methods. The results obtained suggest that the combination B3LYP/6-31G(d,p): PM3 makes it possible to predict the good minimum of energy.

The natural bond orbital analyses (NBO) were applied as a powerful approach for the evaluation of the intermolecular interactions between the two molecules (Table 2). Analysis of the NBO calculations, carried out using the DFT method with the functionalities mentioned above, show that no hydrogen bonding was established between procaine and β-CD. This result was expected since the amino group ($-NH_2$) which is deeply inserted into the cavity interacts weakly with the atoms of the CD as evidenced by the low values of the interaction energy (0.08 to 0.18 kcal mol^{-1}). These values are far from ones usually are reported for hydrogen bond energies. Concerning the benzyl ring, this group does not contain electronegative heteroatoms and hence no hydrogen bonds are expected. As a result, only the Van der Waals forces are responsible for the stability of the complex formed as shown by the results of the NBO calculations in Table 2. This can be noted by the existence in one hand of a charge transfer between occupied NBOs (donors) σ(CH) and unoccupied NBOs (acceptors) σ* (CH) of the benzyl ring and in the other one of NBO acceptors σ* (CH) and NBO donors σ (CH) of the β-CD cavity.

The values of $E^{(2)}$ energies derived from the NBO calculations are of the order of 2 to 3.2 kcal mol^{-1}, this order of magnitude is considered as a mean energy of a Van der Waals interaction and far from being classified as a strong binding energy (covalent or dative). The results obtained using the functionals M06-2X and B3LYP are less descriptive of the intermolecular interactions of Van der Waals type compared to the results provided by the WB97XD dispersion functional.

The UV-Vis theoretical spectrum of procaine is shown on Fig. 5a. Three peaks centered at absorption wavelength 189.2, 214.7 and 264 nm are observed, which are attributed to the electronic transitions related to NH_2, C=O and functions conjugated to the benzene chromophore. For the procaine/β-CD complex (Fig. 5b), a bathochromic effect is observed corresponding to a displacement of maximum wavelength by 13.5 nm. This results is explained by the fact that the non-binding pairs of nitrogen are protected inside the cavity and do not contribute to the formation of hydrogen bonds with the solvent molecules. This increases the electronic delocalization and reduces the gap energy HOMO/LUMO leading to a displacement of the electronic transitions towards higher wavelengths. The complexation reaction of the procaine then leads to the new electronic transitions resulting from the change in the environment which was polar (water) and became apolar (cavity of the β-CD).

Table 3 reports the chemical shifts of the aromatic protons for the free drug. The aromatic protons Hb and Hb' located close to the CO attractor group are less shielded with regards to Ha and Ha' ones situated at ortho position. When the complexation with β-CD occurs, both chemical shifts and line broadening take place especially for Ha and Ha' aromatic protons as shown in the spectrum (Fig. 6). A variation of 0.08 ppm is found for Ha and Ha' protons whereas only 0.01 ppm displacement is noted for Hb and Hb' ones. Thus, combined with the observed variation in chemical shifts of the CD cavity H3 and H5 protons, it is justified to conclude that the procaine molecule penetrates by its primary amino-end into the β-CD cavity.

Table 2. Van der Waals Interactions Energies, $E^{(2)}$, between Procaine and β-CD

NBO donor	NBO acceptor	
Procaine donor and β-CD acceptor		M06-2X/6.31G(d,p) (kcal mol^{-1})
σC152-H154	σ*C35-H116	2.54
σC153-H155	σ*C11-H89	2.77
β-CD donor and procaine acceptor		
σC9-H87	σ*C157-H159	2.61
Procaine donor and β-CD acceptor		B3LYP/6-31(d,p) (kcal mol^{-1})
σC_{152}-H_{154}	σ^*C_{35}-H_{116}	2.28
σC_{153}-H_{155}	σ^*C_{11}- H_{89}	2.99
β-CD donor and procaine acceptor		
σC_9-H_{87}	σ^*C_{157}-H_{159}	2.50
σC_{33}-H_{114}	σ^*C_{156}-H_{158}	2.26
σC_{39}-H_{121}	σ^*C_{167}-H_{168}	2.80
Procaine donor and β-CD acceptor		WB97XD/6-31(d,p) (kcal mol^{-1})
σC_{152}-H_{154}	σ^*C_{35}-H_{116}	2.91
σC_{153}-H_{155}	σ^*C_{11}-H_{89}	3.17
σC_{157}-H_{159}	σ^*C_9-H_{87}	2.39
β-CD donor and procaine acceptor		
σC_9-H_{87}	σ^*C_{87}-H_{159}	2.91

Table 3. Chemical Shifts δ of Protons Ha, Ha' of Procaine Hydrochloride and H3, H5 of ß-CD, and the Variations of the Chemical Shifts Δδ due to the Complexation Reaction

Protons	δ (ppm)	Δδ (ppm)
Ha, Ha'	6.663-6.693	0.08
H3	3.843	0.1
H5	3.727	0.2

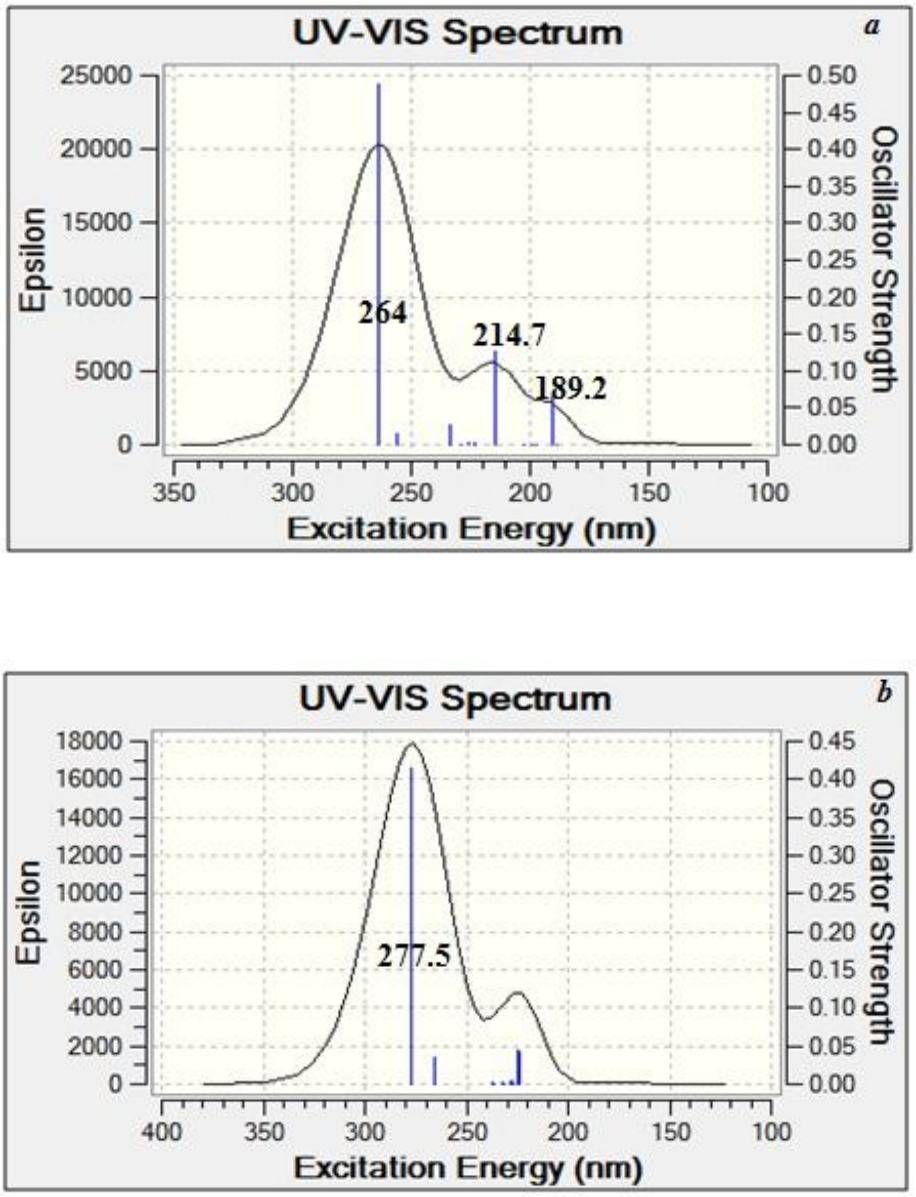

Fig. 5. TD-DFT calculated absorption spectra of free procaine (a) and complex (b).

CONCLUSIONS

This work reports a study of the complexation of procaine by β-CD. The overall image of the results indicates that procaine hydrochloride enters by its secondary amine group into the cavity of β-CD forming a 1:1 stoichiometry inclusion complex. The best global minimum is obtained by the ONIOM method (B3LYP/6-31G(d,p):PM3). The thermodynamic data show that the complex formed is well structured. The analysis by natural bond orbital (NBO) shows that the types of interactions responsible for the stability of the complexes formed are of Van der Waals forces types. This result is confirmed by 1D ^{1}H NMR spectroscopy.

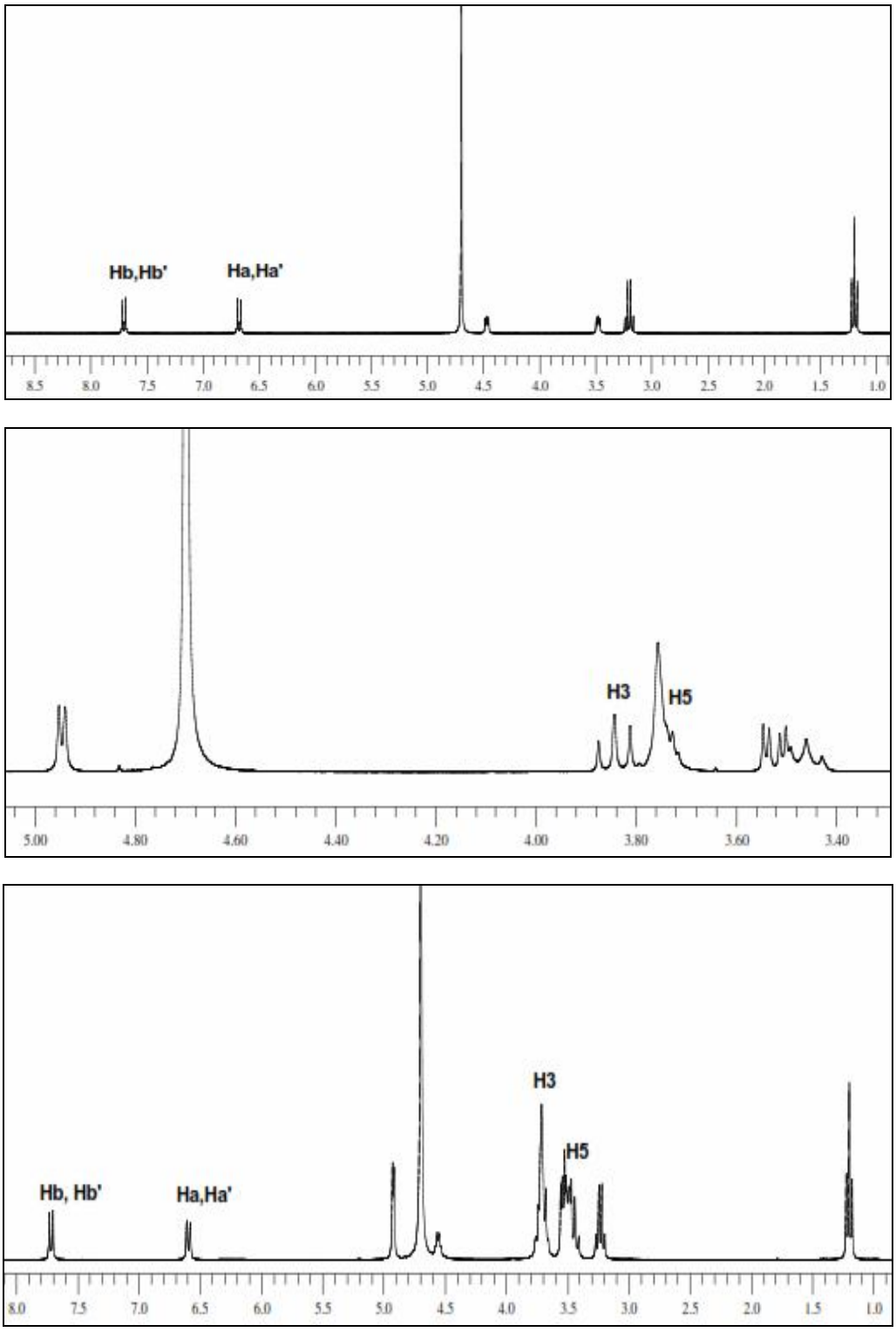

Fig. 6. ^{1}H NMR signals for Ha, Ha', Hb and Hb' protons of free procaine (a), H3 and H5 of free β-CD (b) and procaine bound with β-CD (c).

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