Theoretical Study of the Complexation of Lidocaine by α- and β-Cyclodextrins.

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Summary: Structure and stability of an eventual inclusion complex formed by Lidocaine and two cyclodextrins (α- and β-CD) were investigated using molecular mechanics and quantum-chemical methods in the gas phase and in water. The molecular docking and quantum chemical calculations results show that no inclusion complex is formed between α-CD and Lidocaine molecule, while the conformational research allowed observing two minimum-energy structures between this molecule and β-CD. From a potential energy scan, a partial inclusion of the two ends of Lidocaine by the secondary face of the cavity of β-CD is observed with a better stability for the complex including the ((-$N(C_2H_5)_2$) group in it. The minimum energy conformers, obtained by semi empirical method (PM3), have been exposed to fully geometry optimization employing ONIOM2 calculations by combining PM3 method with B3LYP, M06-HF and WB97XD functionals at 6-311G (d,p) basis set. The results show that complexation reactions are thermodynamically favored ($\Delta G° < 0$) and the inclusion complexes are energetically stables and well structured ($\Delta S° < 0$). According to the analysis of natural bond orbitals, the Van der Waals interactions are the sole driving forces that ensure the stability of the formed complexes.

Keywords: Inclusion complex, Lidocaine, Cyclodextrins, Molecular docking, PM3, NBO.

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides produced during the enzymatic degradation of starch induced by CGTase (CyclodextrinGlycosyl Transferase) followed by an intra-molecular trans-glycosylation reaction [1,2]. They are truncated cone-shaped molecules constituted of a variable number of a chair conformation α-D-glucopyranose units inter linked in α(1,4) position. Depending on the number of these units, one distinguishes (α-CD), (β-CD) and (γ-CD) which contain respectively 6, 7 and 8 units per molecule and possess therefore different rim diameters (Fig. 1a). These three CDs are known as "native cyclodextrins" but other CD-derivatives exist and were synthesized to enhance the solubility of the native ones in water or to optimize their pharmaceutical use as excipient. In fact, CDs and their derivatives have the capacity to form inclusion complexes of Host-Guest type with various low aqueous solubility molecules that fit adequately the size cavity of the CD [3-5]. The formation of these inclusion complexes is accompanied by the replacement of the internal water molecules in the CD hydrophobic cavity by the guest molecule. Other than the rim size, the favorable binding is obtained according to the balance between electrostatic, Van der Waals, and hydrophobic forces as well as hydrogen bonds [6-8]. In pharmaceutical area, using CDs as drug delivery systems, allows a delayed release of drugs, resulting in a longer duration of action with an improvement in its chemical and physical properties [9]. This work deals with the ability of two CDs (α, and β-CD) to encapsulate an active ingredient widely used in the surgical field. The guest molecule is the Lidocaine; an amino-amide type local anesthetic (Fig. 1b) which utilization is often accompanied by uncomfortable side effects [10, 11].

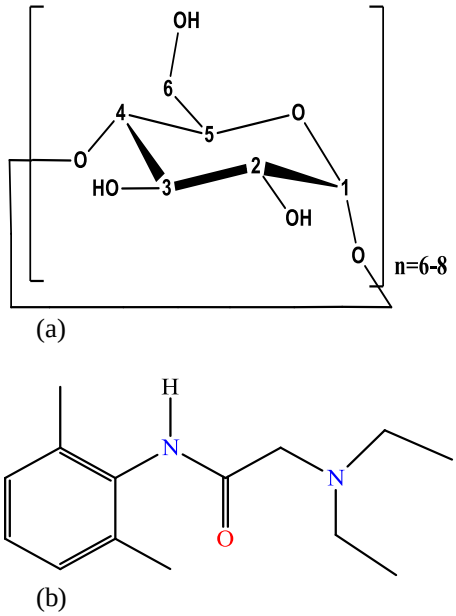

Fig.1: Structures of (*a*) α-, β-CD and (*b*) Lidocaine.

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The experimental works conducted to explore the complexation reaction between CD and Lidocaine haven't provided enough information on the dominant interactions involved, the stability and the architecture of the formed complexes [9,12,13]. Thus, this study aims to tackle these tasks from a theoretical point of view, to show the feasibility of the complex formation, its total energy, stability and the nature of the driving forces in such phenomenon. Thus, 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 CD/Lidocaine. The formed complex obtained at the minimum of the PES is furthermore refined by DFT calculations with different functionals using ONIOM method leaving all the structural constraints free. For examining the effect of solvent on the stability of inclusion complexes this continuum model "the Onsager Cavity Model", referred to as the SCRF Model, for "Self-Consistent Reaction Field" is chosen [14]. Finally, the determination of the interactions involved is possible by analyzing the natural bond orbitals (NBO) which permits a convenient basis for investigating charge transfer in molecular systems [15-18].

Calculations methods

Molecular Docking Simulation

The molecular docking is an attractive strategy for ligand-receptor interaction using molecular mechanics principles. In this study, docking is conducted by using AutoDock4.2 programs to predict the binding energies between Lidocaine and CDs. In docking simulation, Lamarkian genetic algorithm method is utilized to generate possible interactions between rigid receptors (CDs) and the flexible ligand (Lidocaine) already optimized separately by quantum chemical calculation using PM3 method. In order to search favorable interactions energies between the host and the guest molecules, a grid map of dimensions 60Å× 60Å× 60Å with grid spacing of 0.375Å is placed where the host molecule occupies the center of the box. Lidocaine is docked into CDs molecules using the following Cartesian coordinates as the center of the search space: x = 2.5 A°, y = 6.5 A°, and z = 7.5 A°.

Quantum chemical calculations

All calculations were performed by using the Gaussian 09 software package [19]. The initial Lidocaine geometry was built employing Chem Draw program software and that of β-CD were extracted from ChemBio3D Ultra (version 13.0, Cambridge software). The structures of Lidocaine, α-CD, and β-CD were subjected to a geometry optimization by semi empirical method PM3 [20]. For all the starting structures frequency calculations were carried out to confirm the completeness of optimization (no negative Eigen values of the Hessian matrix). The insertion pathway is directed along the Z-axis where the Lidocaine molecule penetrates inside the hydrophobic cavity of these two CDs with a step of 0.25 Å with no constraint but the CDs structures are kept frozen. For the Insertion process, two possible orientations exist to enable Lidocaine to enter inside the α- or β-CD's cavity. In the first orientation, the Lidocaine penetrates with its aromatic moiety first through the wider rim of these two CDs (Fig. 2), and in the second one it is inserted with its iso-ethyl fragment front. In both cases, the insertion is performed until obtaining an energy minimum. However, the real energetic minimum corresponds to the minimum of which the atoms of CD are not frozen, it is then necessary to release completely the structure of the complex to have the true minimum. Harmonic frequency calculations were also computed for the obtained inclusion complexes to confirm them as true minima on the potential energy surface.

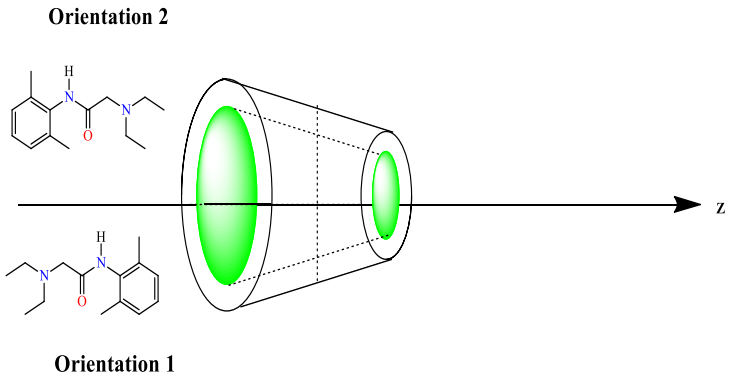


Fig. 2: Inclusion of Lidocaine into α-, and β-cyclodextrins.

Next, in an attempt to refine the results, we have carried out geometry optimization for the minimum energy structures using the ONIOM method [21], in which, we combine a semi empirical method (PM3) and the density functional theory DFT with three hybrids functional. 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-HF: a functional belongs to the family of functionals developed by Zhao and Truhlar at the university of Minnesota [22], used to predict the charge transfer. The basis set used in this section of calculation is 6-311g (d,p). The whole system (complex) is divided in two level systems, the model (Lidocaine) and the real system (complex). The ONIOM energy is evaluated as:

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

To quantify the interaction between host and guest in the optimized geometries, we have evaluated complexation and binding energies using the following equations:

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

$$E_{binding} = E_{complex} - E\,(Lidocaine)_{sp} - E\,(CD)_{sp} \quad (3)$$

where $E_{complex}$, E^{opt} (β-CD) and E^{opt} (Lidocaine) in equation 2 denote, respectively, the energies of the optimized geometries of the 1:1 complex, the free host molecule (β-CD) and the free guest molecule (Lidocaine). $E\,(Lidocaine)_{sp}$ and $E\,(CD)_{sp}$ are the single point energies of free guest and the host molecules in the complex.

The method of natural bonding orbitals (NBO), implemented in the Gaussian program, makes it possible to describe Van der Waals forces and hydrogen bonds according to the Lewis model, by choosing the right calculation method. In this method, the charge transfer results from Lewis-type occupied NBOs (donors) and unoccupied NBOs (acceptors) is estimated by the second-order perturbation theory, whose stabilization energy is defined by equation (4) [23]:

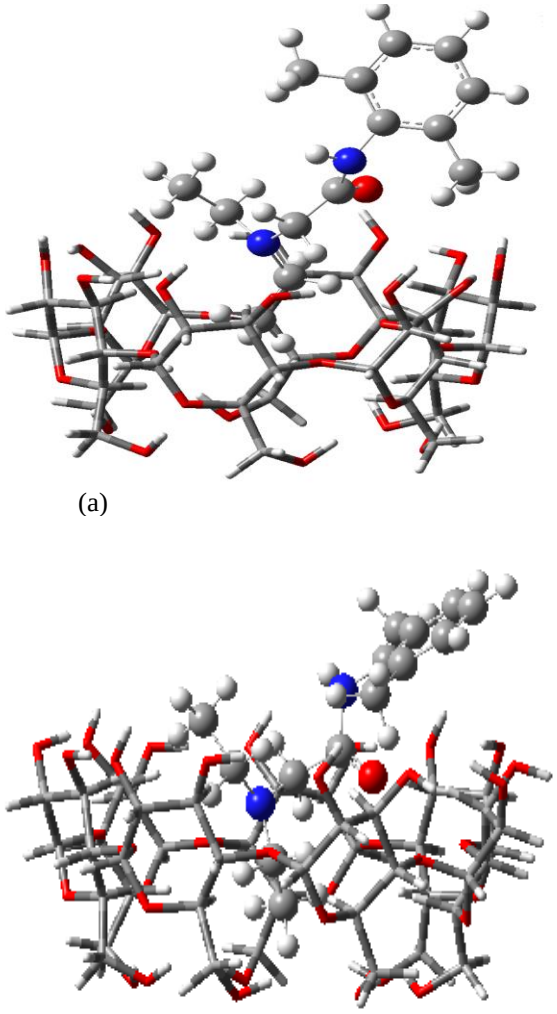
$$E^{(2)} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i} \quad (4)$$

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

Results and discussion

Molecular Docking results

Fig.3*a* shows the structures of the association Lidocaine:α-CD complex (*a*) and the inclusion Lidocaine:β-CD complex (*b*) obtained from Docking experiments. It is easy to note that Lidocaine is successfully docked in the β-CD cavity while its inclusion in the cavity of α-CD is inhibited by the steric effect. It is obvious to claim that the relatively small diameter of the α-CD cavity hinders the inclusion process underlying a non-adequacy between the shape of the cavity of this CD and the size of the Lidocaine. However, the structure of the inclusion complex obtained during the molecular docking process shows that Lidocaine partially penetrates through its $(-N(C_2H_5)_2$ end into the cavity of β-CD (Fig. 3*b*).



(a)

(b)

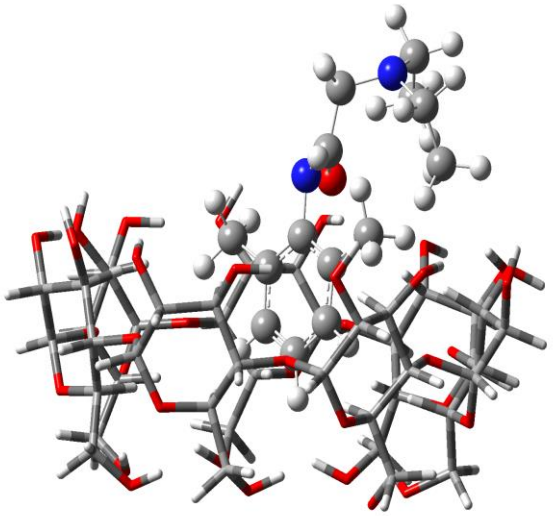
Fig. 3: Structures of (*a*) the Lidocaine:α-CD association and (*b*) the Lidocaine:β-CD inclusion complex obtained by the docking procedure.

The best conformation of the formed inclusion complex have been subject to optimization by PM3 method (single point optimization), which allows the evaluation of the complexation energy -6.91 Kcal/mol. Due to the lack of any new covalent bonds, the stability of the inclusion complex is controlled by low energy forces.

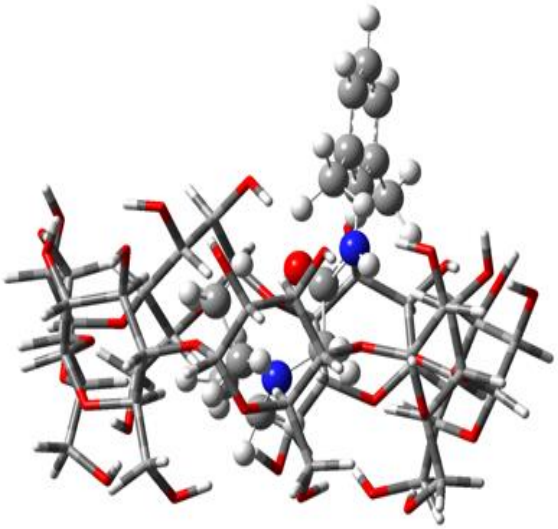
Results of quantum chemical calculations

Structure Optimization of the free reagents namely Lidocaine, α- and β-CDs by PM3 method led to the best starting geometries confirmed by the frequency calculation and the negative values of the energies. No minimum occurred during the interaction between Lidocaine and α-CD, in agreement to molecular docking results. The absence of such complex means that the size of the α-CD (secondary rim internal diameter = 4.7 Å) does not favour the penetration of the Lidocaine. In the case of β-CD, a minimum is observed for each orientation which confirm the inclusion of the two ends of the Lidocaine into the cavity of this CD. The negative complexation energy values obtained for all the steps of the PES curve mean that the complex structures are more stable with respect to the corresponding starting structures. These results are in agreement with experimental observations reported by Pinto *et al*. [12] and Abou-Okeil [9], but is in contradiction with conclusion of Soni and Pal [13] who claimed that Lidocaine forms a complex with α-CD with equilibrium constant K = 238 M^{-1}. The architecture of the complexes formed illustrated in figure 4 shows that the penetration of the benzyl ring is not complete due to the presence of two methyl groups in the ortho position preventing the complete inclusion of this ring. This result suggests that the host: guest association will be limited and a full penetration of the benzyl ring of this drug is probably possible with a larger diameter cavity like that of γ-CD. For the second orientation case, the (-N $(C_2H_5)_2$ group is also included into the cavity of the β-CD.

The results obtained from the SCAN calculations and those obtained by the ONIOM method are gathered in Table 1. The two orientations produce two complexes which are close energetically in terms of complex energy and complexation energy but different on basis of the HUMO-LUMO gap. The same statement is observed for rest of the thermodynamic parameters as well as ONIOM energies obtained. From a thermodynamic point of view, it appears that the complexation reactions are exothermic ($\Delta H° < 0$) and thermodynamically favored ($\Delta G° < 0$). Moreover, the negative values of the entropy variation show that the complexation processes lead to well structured systems. The energy quantities obtained during the ONIOM calculations indicate that the good energy minima are obtained by using the combination B3LYP/6-311G(d,p):PM3, the latter can then be considered as the right choice for optimizing the structures of supramolecular compounds with reduced time and good quality results.



(a)



(b)

Fig. 4: Structures of Lidocaine:β-CD complexes for (*a*) orientation **1** and (*b*) orientation **2.**

When the solvation effect is taken into account, the energy of complexation becomes lower (-14 Kcal/mol) and the HOMO / LUMO difference becomes more significant for the two orientations. The solvent is then a factor favoring the complexation reaction and can positively affect the stability of the

inclusion complex. The results obtained by the NBO calculations, using the DFT method and the functionalities mentioned above, make it possible to investigate the type of stabilizing forces (Table-2).

Table-1: Energy and thermochemical quantities of the Lidocaine β-CD complex.

Complex 1:1 (Lidocaine:β-CD)	Orientation 1	Orientation 2
Complex energy PM3 (Kcal/mol)	-1504.37 -1524.21(*)	-1504.98 -1524.3(*)
Complexation energy (Kcal/mol)	-7.11	-7.73
HOMO / LUMO gap (eV)	9.22 9.43(*)	11.68 11.9(*)
Interaction energy (Kcal/mol)	-16.16 -16.66(*)	-15.98 -16.01(*)
ΔrS (cal/K.mol)	-64.65 -64.99(*)	-68.03 -68.43(*)
ΔrH° (kcal/mol)	-22.52 -22.7(*)	-23.27 -23.48(*)
ΔrG° (kcal/mol)	-3.25 -3.33(*)	-3.00 -3.09(*)
E ONIOM [B3LYP/6-311G(d,p): PM3] (Kcal/mol)	- 466239.34	-460599.81
E ONIOM [M06HF/6-311G(d,p): PM3] (Kcal/mol)	- 460449.54	-460449.34
E ONIOM [wB97XD/6-311G(d,p): PM3] (Kcal/mol)	- 460445,55	-460452.38

(*) Energetics values obtained with PCM model of solvation

Analysis of these results confirms that no intermolecular hydrogen bond is established for the orientation 1 because the included benzyl ring does not contain electronegative hetero-atoms. Likewise for orientation 2, no hydrogen bridge is established because the nitrogen atom of Lidocaine stays far from the hydrogen atoms carried by the oxygen of β-CD, thus no hydrogen bond contribution occurs for the two complexes. Therefore, only the Van der Waals forces are responsible for the stability of the formed complexes as shown by the results of the NBO calculations. Several sites of intermolecular interactions have been reported on Table-2, these are evaluated in terms of charge transfer for the two orientations. The bonds which ensure this transfer of charge are the C-H bonds of the β-CD directed towards the interior of the cone; *i.e*. the H_3 and H_5 protons of the cavity of this CD and the C-H bonds of the methyl's linked to the benzyl ring (orientation 1) and the C-H bonds of the group (-N $(C_2H_5)_2$ for the orientation 2. The most significant energy values $E^{(2)}$ are of the order of 2-2.65 Kcal/mol, weak values which facilitate the release of Lidocaine in the Human body, an important property in drug formulation. The WB97XD functional gives a good estimate of the $E^{(2)}$ interaction energies of distant atoms and therefore a good description of long-range interactions (dispersion phenomena).

Table-2: $E^{(2)}$ interaction energies between Lidocaine andβ-CD.

NBO donor NBO acceptor	Orientation 1
Lidocaine donor and β-CD acceptor	M06HF /6.311G (d,p) (Kcal/mol)
σ C157 - H162 σ* C9 – H87	2.17
Lidocaine donor and β-CD acceptor	B3LYP/6-311(d,p) (Kcal/mol)
σ C157 - H162 σ* C9 – H87	2.19
σ C158 - H165 σ* C27-H107	2.08
Lidocaine donor and β-CD acceptor	wB97XD/6-311(d,p) (Kcal/mol)
σ C157 - H162 σ* C9 – H87	2.65
σ C158 - H165 σ* C27-H107	2.29
NBO donor NBO acceptor	**Orientation 2**
Lidocaine donor and β-CD acceptor	M06HF /6.311G (d,p) (Kcal/mol)
σ C149 - H159 σ* C23 – H102	2.14
Lidocaine donor and β-CD acceptor	B3LYP/6-311(d,p) (Kcal/mol)
σ C155 - H157 σ* C35 – H116	2.0
Lidocaine donor and β-CD acceptor	1.96
σ C15 – H93 σ* N168-H169	
Lidocaine donor and β-CD acceptor	wB97XD/6-311(d,p) (Kcal/mol)
σ C149 - H159 σ* C23 – H102	2.61
σ C149 - H160 σ* C29-H109	2.12
σ C151 - H153 σ* C27-H107	2.01
σ C163 - H164 σ* C17-H95	2.0
σ C163 - H165 σ* C11-H89	2.04
σ C177 - H182 σ* C3-H80	2.17
β-CD donnor and Lidocaine acceptor	
σ C15 – H93 σ* N168-H169	2.07

Conclusion

The work carried out reports a computational study on the complexation reaction of Lidocaine by α-, and β-CD. The objective was to investigate whether or not inclusion complexes form and to examine the interactions that promote such complexes. The overall sight of the results indicates that docking of Lidocaine into the α-CD cavity is not allowed due to the small diameter of this CD, while this drug forms 1:1 stoichiometric inclusion complexes with β-CD. The best global minimum is obtained by including the ((-N $(C_2H_5)_2$) part in the cavity of the β-CD as shown by the energy calculation performed by the ONIOM method (B3LYP/6-31G(d,p):PM3). The thermodynamic data show that the complexes formed are well structured

and the complexation reaction is thermodynamically favored. The analysis by natural bond orbital (NBO) shows that only Van der Waals forces are responsible for the stability of the formed complexes.

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