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FIRST PRINCIPLES SIMULATIONS OF MANGIFERIN INTERACTING WITH BETA-CYCLODEXTRIN[1]

SIMULAÇÃO DE PRIMEIROS PRINCÍPIOS DA MANGIFERINA INTERAGINDO COM BETA-CICLODEXTRINA

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ABSTRACT

The structural and electronic properties of the mangiferin molecule interacting with the molecule beta-cyclodextrin (beta-CD) are investigated. In this work we used *ab initio* calculations using the SIESTA Code. The results show a weak interaction of mangiferin molecules when absorbed on the external fragment and a stronger interaction when introduced at beta-CD's cavity. These adsorptions cause minor changes on the electronic structure, making the weak interaction interesting in the chemical and biological point of view. In this work the interaction of beta-CD with mangiferin molecule was performed through *ab initio* simulations using the SIESTA Code. The complex between mangiferin and beta-CD is kept associated without altering the structural properties of the drug with original active principles, thus indicating that it can be removed from beta-CD.

Keywords: *ab initio* calculations, DFT, SIESTA.

RESUMO

As propriedades estruturais e eletrônicas da molécula de mangiferina interagindo com a beta-ciclodextrina (beta-CD), são investigadas. Neste trabalho utilizamos cálculos ab initio através do código SIESTA. Os resultados obtidos demonstraram que as moléculas de mangiferina apresentaram interação fraca quando adsorvido na parte externa da beta-CD e interação forte quando introduzida na cavidade da beta-CD. Esta adsorção causa pequenas alterações na estrutura eletrônica, tornando a interação fraca interessante no ponto de vista químico e biológico. O complexo entre mangiferina e beta-CD é mantido associado, sem alterar as propriedades estruturais do fármaco original, indicando assim, que o mesmo pode ser removido da estrutura da beta-CD.

Palavras-chave: *cálculos ab initio, DFT, SIESTA.*

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INTRODUCTION

Mangiferin is an active phytochemical present in various plants, including *mangifera indica L with chemical structure 1,3,6,7-tetrahydroxy-2-[3,4,5-trihydroxy-6--(hydroxymethyl)oxan-2-yl] xanthen-9-one* (DAS et al., 2012; SINGH et al., 2012). This molecule has several medicinal properties, such as antiviral, antioxidant, antibacterial, anti-diabetic, anti-allergic, anti-inflammatory, anti-diarrheal, anti-tumor, anti-HIV, among others (SOUZA et al., 2009).

However, mangiferin presents low solubility in aqueous medium (less than 0,111 $mg.mL^{-1}$); which hinders its absorption and the subsequent bioavailability. One strategy to increase its solubility and thus its therapeutic efficacy would be its complexation with cyclodextrins (CD). In this way, it is possible to preserve the chemical structure of the molecule and increase the bioavailability of substrates with poor solubility in water, and, subsequently, prolong the time in the human body (FERREIRA et al., 2013; SOUZA et al., 2009).

Due to its properties, the CDs are being widely used as drug carriers (FERREIRA et al., 2013). These are cyclic oligosaccharides composed of glucose units with an outer [inner] hydrophilic surface [hydrophobic cavity], allowing the formation of inclusion complexes with lipophilic substances that increase their solubility in water (LOFTSSON; BREWSTER, 1996). In addition, increasing water solubility and its efficiency, the CD protect drugs against oxidation, hydrolysis, photo-decomposition, loss by volatility, heat and unwanted organoleptic characteristics, increasing its stability (BRITO et al., 2004).

The most common CD that are naturally occurring are alpha-CD, beta-CD, gamma-CD, consisting of 6, 7 and 8 glucose units, respectively, which adopt chair conformation. The minimum criterion for the complex formation is the compatibility of sizes and geometries between the cavity of the CD and the guest compound (OLIVEIRA et al., 2009). That compatibility sizes may not correspond to the entire molecule, and only as a part of the guest can be included in the cavity (ARUN et al., 2008; STELLA; HE, 2008).

The molecular structure of beta-CD becomes more useful due to the drugs carrier possibility attached with the low toxicity, the cavity size (from 0.60 to 0.65 nm) and low cost (SZEJTLI, 1990). In contrast, beta-CD has a low aqueous solubility, which can be overcome by raising the temperature or using organic solvents (methanol or ethanol, below 30%) (ARUN et al., 2008; SZEJTLI, 1998).

Thus, considering the contribution of beta-CD systems for drug delivery, in this work, the structural and electronic properties of the beta-CD molecule interacting with mangiferin is evaluated by first-principles calculations.

MATERIALS AND METHODS

The interaction between mangiferin molecule and beta-CD was evaluated through *ab initio* simulations based on the density functional theory (KHON; SHAM, 1965). The calculations were

done using the SIESTA code (Spanish Initiative for Electronic Simulations with Thousands of Atoms) (SOLER et al., 2002) that perform self-consistent simulations, solving the Kohn-Sham with atomic numerical orbitals as basis set (double-zeta plus polarization function - DZP, with energy shift of 0.05 eV) (BEVILAQUA et al., 2010; VENDRAME et al., 2013).

To represent the charge density a cutoff radius of 200 Ry (SOLER et al., 2002) for the energy mesh interaction in real space was used. The exchange-correlation potential was treated within the local density approximation (LDA) (PERDEW; ZUNGER, 1981). All geometry optimizations were performed with total relaxation of all atoms of beta-CD as well as the mangiferina molecule (convergence criterion on all atomic coordinates of 0.05 eV/Å) (BEVILAQUA et al., 2010; VENDRAME et al., 2013).

The binding energy (E_b) was calculated using the basis set superposition error (BSSE) (BOYS; BERNARDI, 1970) as reported on the equation (1):

$$E_b = - [E_T(\text{beta-CD+ mang}) - E_T(\text{beta-CD}_{ghost} + \text{mang}) - E_T(\text{beta-CD} + \text{mang}_{ghost})] \quad (1)$$

Which E_T (beta-CD+ mang) is the total energy of the resulting complex, E_T (beta-CD_{ghost} + mang) [E_T (beta-CD + $mang_{ghost}$)] is the total energy of the isolated mangiferina [beta-CD] molecule.

RESULTS AND DISCUSSION

The structural and electronic properties of the beta-CD interacting with mangiferin were evaluated. The equilibrium geometries and the energy levels for mangiferin and beta-CD are shown in figures 1 (a) and (b), respectively.

First, the structures of the beta-CD and the mangiferin were optimized with full relaxation of the atoms. It can be observed, as shown in figures 1 (a), a difference between HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) of 4.84 eV for the beta-CD. In figure 1 (b) we also observe a difference HOMO and LUMO of 2.45 eV for the isolated mangiferin molecule.

Different configurations of beta-CD interacting with mangiferin were analyzed and the most stable ones are shown in figure 2. The arrangements are described as β-CD-mang-I: the oxygen atom of mangiferin near the hydrogen atom of the beta-CD; β-CD-mang-II: the hydrogen atom of mangiferin interacting with the oxygen atom of the CD; β-CD-mang-III: the oxygen atom of mangiferin close to the hydrogen atom of the beta-CD; β-CD-mang-IV and β-CD-mang-V: mangiferin molecule in the inner cavity of beta-CD; β-CD-mang-VI: the mangiferin molecule parallel to the cavity of the beta-CD.

Figure 1 - Structural configuration and electronic levels for (a) beta-CD and (b) mangiferin molecule.

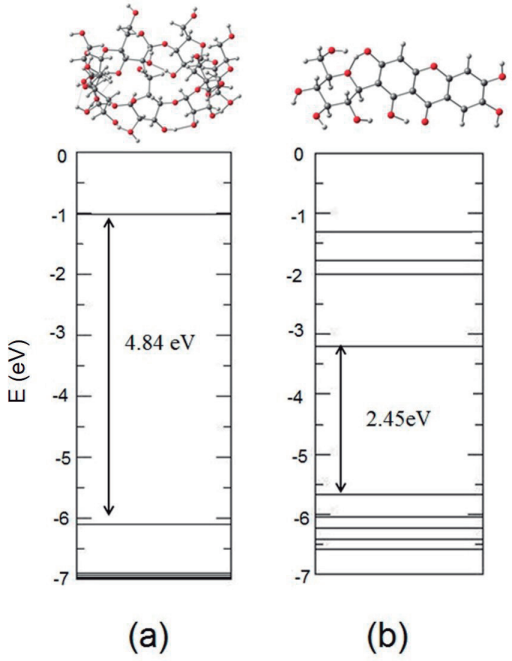
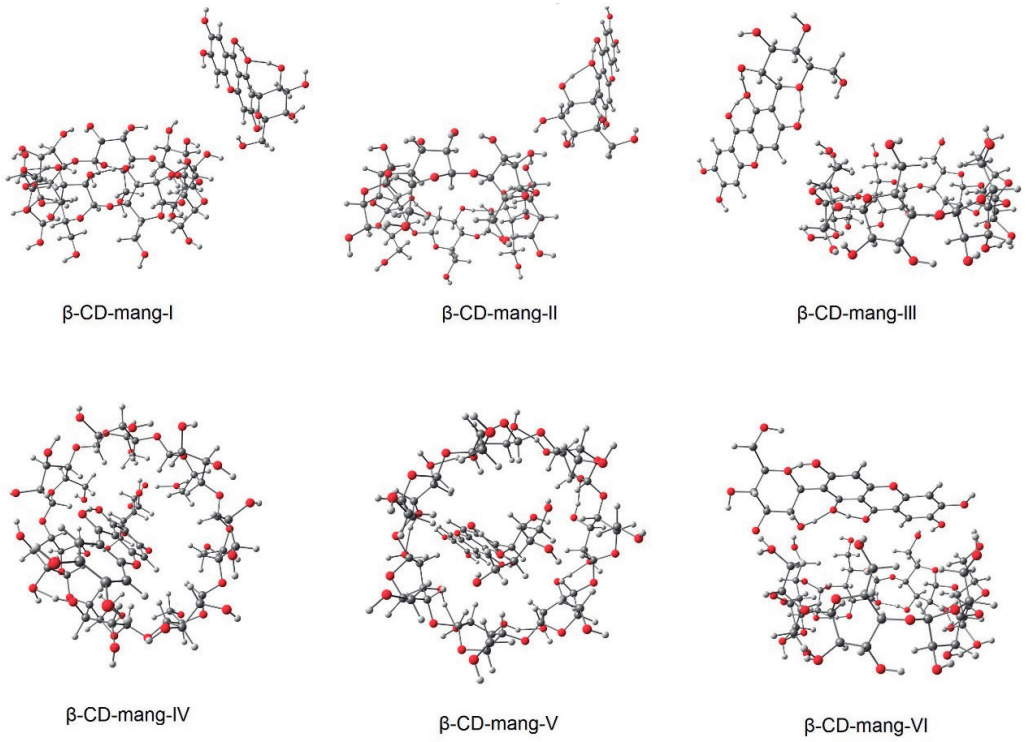


Figure 2 - Structural configurations of beta-CD interacting with the mangiferin molecule.



In table 1, it is possible to observe, for all configurations studied, the values of the binding energies, distances of relevant molecular bounds and charge transfer. The most stable complex for the mangiferin molecule in the outer surface of beta-CD is the configuration β-CD-mang-III with binding energy of 0.47 eV. For inner configurations, the most stable one is the β-CD-mang-V with binding energy of 3.24 eV.

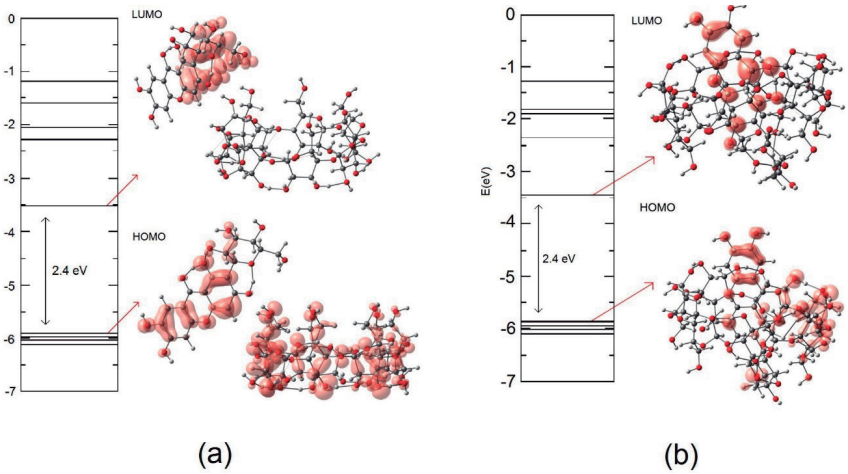
Table 1 - Interatomic distances, binding energy (E_b), and charge transfer (Dq) for the studied configurations of mangiferin and beta-CD (positive values for the charge transfer indicate that the beta-CD is an electron acceptor).

Configuration	Interatomic distance (Å)	E_b (eV)	Dq (e^-)
β-CD-mang-I	1.73 ($H_{\beta CD}$ -O_{mang})	0.32	0.10
β-CD-mang-II	1.71; 1.63 ($H_{\beta CD}$ -O_{mang})	0.33	0.02
β-CD-mang-III	1.64 ($O_{\beta CD}$ -H_{mang})	0.47	0.05
β-CD-mang-IV	1.76; 1.61	2.75	-0.45
β-CD-mang-V	1.65	3.24	-1.03
β-CD-mang-VI	1.56	2.10	-0.04

We observe that the binding energy values for the mangiferin-CD complex differ substantially depending if the molecule is in the outer or inner surface of the CD. These results can be understood because the mangiferin encapsulated on the inner of CD increases the number of molecular bonds between the systems

Figures 3(a) and (b) show the electronic levels and the plot for the local electronic charge density for the configuration β-CD-mang-III and β-CD-mang-V, respectively. A reduction in the HOMO-LUMO gap is observed for both configurations when these complexes were compared with the beta-CD isolated. This reduction is due to the appearance of new electronic levels resulted from the interaction.

Figure 3 - Electronic levels and plot for the localized density of electronic charge for the most stable configurations (a) β-CD-mang-III and (b) β-CD-mang-V.



Furthermore, the plots of electronic charge density for the LUMO (Figure 3 (a)) show a contribution on the mangiferin and a distribution in the HOMO for the mangiferin molecule as well as beta-CD. From the Mulliken population analysis, the charge transfer systems studied show that the CD behaves as an electron acceptor for mangiferin interacting on outer configurations of beta-CD. Based on the binding energy results for mangiferin adsorbed on the outer surface of the beta-CD

and the low charge transfer between the systems of the complex, we can observe that the interaction occurs through a physical regime.

For the mangiferin interacting with beta-CD via inner surface, the plot of the localized electronic charge density for the most stable configuration (β-CD-mang-V), figure 3 (b) shows a charge contribution on the mangiferin for the HOMO and LUMO. From the Mulliken population analysis for the mangiferin in the cavity of the beta-CD, we can observe that the charge transfers occur from the beta-CD to the mangiferin molecule. It can be observed that the interactions of mangiferin in the internal cavity occurs through a strong interaction that can be corroborated by the high values of binding energy and charge transfer (around 1 electron for the configuration β-CD-mang-V), i.e. by a chemical regime.

It is important to note that the most stable configurations vary depending on the structural configuration of mangiferin molecule with beta-CD. This is due to the different approaches between the molecules, reverting to a different number of molecular bounds resulting complexes with a smaller/larger binding distance. Furthermore, the binding energy values show, in the outer of the cavity adsorption, a physisorption process, which is interesting for drug delivery systems.

CONCLUSIONS

The interactions of beta-CD with mangiferin were investigated using first-principles calculations. From the Mulliken population analysis, it was observed that the charge occurred showing that the beta-CD behaves both, as a donor as well as the electron acceptor, for inner and outer configuration of mangiferin on the beta-CD cavity, respectively. In the cases where the mangiferin molecule is introduced into the cavity of beta-CD a strong interaction occurred, suggesting that these configurations are not interesting for drug carrier systems. Based on these results, it is concluded that the CDs can interact with mangiferin and come to form inclusion complexes, and in some cases had low binding energies unchanging their original active ingredients. For this type of interaction, it is extremely interesting that the absorbent system remains connected to its corresponding carrier without changing the original molecules.

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