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Encapsulation process of *p*-Cymene into β-Cyclodextrin: A Theoretical Study.

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Abstract: A theoretical study using semi-empirical (PM3) and DFT calculations (B97D) was performed in both gas and aqueous phases, in order to obtain structural and energetic properties for the encapsulation process of *p*-Cymene into β-cyclodextrin. Two modes of inclusion were assumed for the [*p*-Cym…β-CD] *host-guest* complex: (i) Mode A, when the guest is placed in the hydrophobic cavity of the CD by the wider rim; (ii) Mode B, when the guest is included by the inner rim. As result, we have shown that Mode A complex is slightly more favorable than the Mode B. This fact can be explained by the inclusion depth of *p*-Cym which favors the rise of dispersive forces inside de host cavity.

Key-words: *p*-Cymene, β-cyclodextrin, *host-guest* complexes.

The *host–guest* complexes of bioactive molecules with cyclodextrins (CDs) have been extensively studied and utilized to improve their solubility, dissolution rate, and bioavailability of poorly water-soluble drugs [1]. CDs can increase the aqueous solubility, chemical reactivity, and spectral properties of numerous lipophilic drugs which are used as guest molecules, without changing their intrinsic ability to permeate lipophilic membranes. *p*-Cymene (*p*-Cym) is a naturally-occurring aromatic organic compound also named *p*-isopropyltoluene [2]. It is classified as a hydrocarbon related to a monoterpene and one of the main constituents of the essential oil from species of Protium, with more than 80% of these species found in the Amazon region. Besides, *p*-Cym is an important intermediate used in pharmaceutical industries and for the production of fungicides, pesticides, as flavoring agent. However, due to its lipophilic chemical structure, the *p*-Cym presents low solubility in many polar solvents, as water. In this sense, a new *p*-Cym/CD formulation may provide desirable pharmacokinetic and pharmacodynamics effects such as improvement of drug solubility. The formation of *host-guest* inclusion complexes involving *p*-Cym and CD has been studied experimentally [3]. However, in all of these works, no information about the topology of the complex and thermodynamic properties was provided. In this context, in the present work we carried out a theoretical study of the molecular inclusion process involving the *p*-Cym and β-CD. Our main goal was to understand, at the molecular level, the structural and energetic factors that influence the formation of such complex and its physicochemical properties. Semiempirical (PM3) and DFT (B97D/6-31G(d,p)) calculations were performed in order to obtain reliable structures and thermodynamic properties. Within the quantum

mechanical formalism the solvent effect (water) was taking into account using the polarized continuum model (IEFPCM). Two modes of inclusion were assumed for the [*p*-Cym…β-CD] complex: (i) Mode A, when the guest is placed in the hydrophobic cavity of the CD by the wider rim; (ii) Mode B, when the guest is included by the inner rim. The inclusion complexes were studied considering the 1:1 molar ratio in gas and aqueous phases. All theoretical calculations were carried out using the Gaussian 2009 quantum mechanical package. The main results are summarized in Table 1.

Table 1: B97D/6-31G(d,p)//PM3 complexation energies (ΔE_{compl}) and Gibbs free energy (ΔG) calculated in gas and aqueous phases for the [*p*-Cym…β-CD] inclusion complexes. Values given in kcal.mol^{-1}.

Complexes	$\Delta E_{compl(g)}$	$\Delta G_{(g)}$	$\Delta E_{compl(aq)}$	$\Delta G_{(aq)}$
[*p*-Cym…β-CD] Mode A	-14.71	5.94	-14.17	6.48
[*p*-Cym…β-CD] Mode B	-12.69	6.99	-11.85	7.82

In Table 1, it is possible observe that the ΔE_{compl} and ΔG, both in gas (*g*) and aqueous (*aq*) phases are slightly more favorable for the Mode A complex (Figure 1). The more stability observed for Mode A can be associated to the depth of inclusion *p*-Cym which favors the rise of dispersive forces inside de host cavity. This result is quite relevant once it is the first topological study in literature concerning the formation of such inclusion complex involving *p*-Cym and β-CD.

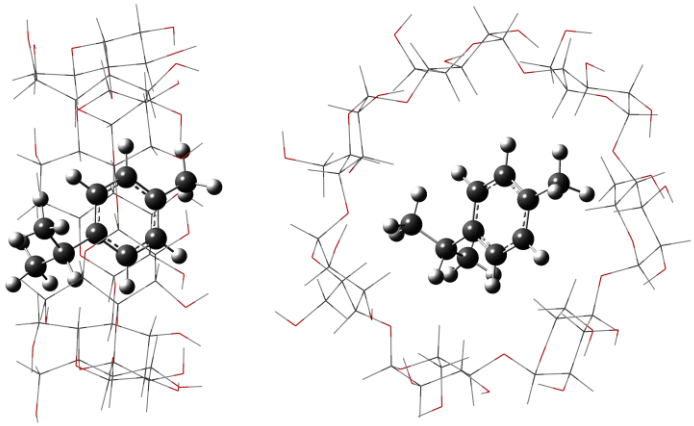

Figure 1: Optimized geometry for [*p*-Cym…β-CD] Mode A complex in two views.

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