

Investigating the Molecular Interactions of Thymol and Menthol as Green Solvents Using DFT Methods †

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Abstract: This research focuses on the study of molecular interactions between two systems known as natural green solvents, thymol and menthol. Their reputation is based on their broad applications in disinfection and consumer products. This analysis concerns the behaviors of these two molecules in the form of dimers. Density Functional Theory (DFT) methods are used in this context. The results show significant interactions between molecules and can help to understand the behavior of one in the presence of the other.

Keywords: thymol; L-menthol; Density Functional Theory (DFT); molecular interactions

1. Introduction

The search for sustainable and environmentally friendly alternatives in various industrial processes has led to a growing interest in green solvents. These solvents, which are derived from natural sources, offer the potential to reduce environmental pollution and promote safer chemical practices. Among the many candidates, thymol and menthol are remarkable for their natural abundance, low toxicity and multiple applications in fields ranging from medicine to food preservation [1].

Thymol (2-isopropyl-5-methylphenol) is well-known for its antimicrobial properties and is widely used in medical disinfection and preservation. On the other hand, Menthol (5-methyl-2-(propan-2-yl)cyclohexan-1-ol) is widely used for its cooling effect and is found in several consumer products, including pharmaceuticals and cosmetics. These two compounds, derived from essential oils, have unique chemical structures that enable them to interact effectively with various substances [2,3]. However, the potential mutual effects of combining thymol and menthol as a solvent system have not been fully explored.

This study explores the conformational stability and interaction energies of thymol and menthol combinations, contributing to a better understanding of green solvents and their potential applications in environmental depollution.

2. Materials and Methods

2.1. Computational Methods

All quantum chemical calculations were performed using Gaussian 09 software [4]. The molecular interactions between thymol and menthol were analyzed using Density Functional Theory (DFT), explicitly employing the B3LYP functional [5,6] combined with the 6-31G(d,p) basis set. This level of theory was chosen for its balance between computational efficiency and accuracy, a balance that was validated in a previous work where it was tested and compared with other methods [7,8].

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2.2. Geometry Optimization

To explore the stability and interactions of thymol and menthol, we performed geometry optimization by testing several dimer combinations of these two systems. We obtained three different dimers, each consisting of two interacting monomers (thymol and menthol), labelled Thym_Ment_1, Thym_Ment_2, and Thym_Ment_3 (Figures 1 and 2). The obtained energies after geometry optimization allowed us to determine their respective stabilities.

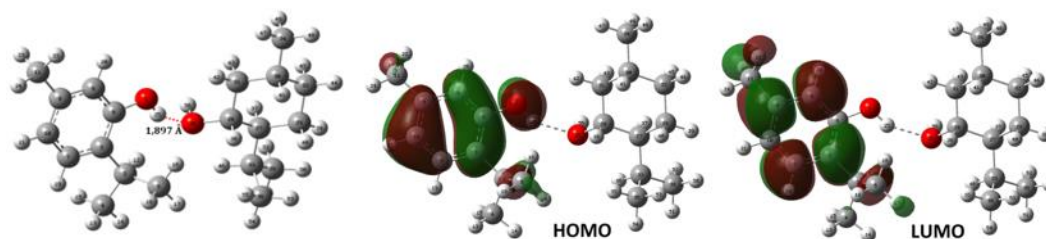


Figure 1. The optimized structure of the Thym_Ment_1 dimer.

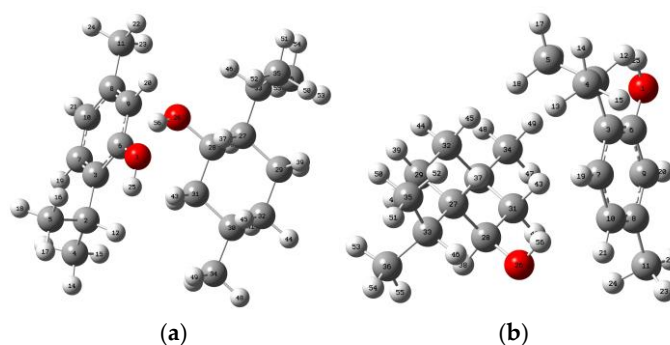


Figure 2. (a) The optimized structure of the Thym_Ment_2 dimer. (b) The optimized structure of the Thym_Ment_3 dimer.

No imaginary frequency was observed. It proves that the three dimers are indeed local minima.

2.3. Single Point Interaction Energy Calculations

After optimizing the dimer geometries, single-point interaction energy calculations were performed to quantify the strength of interactions between the thymol and menthol molecules. These calculations were carried out using the same B3LYP/6-31G** level of theory.

The counterpoise correction method was applied to account for the basis set superposition error (BSSE). Additionally, D3 dispersion corrections were included to accurately capture non-covalent interactions, such as van der Waals forces. The corrected interaction energies were used to evaluate the relative stability of the different dimers.

3. Results and Discussion

In this section, we present the results that were obtained. We compare the electronic energies and corrected complexation energies to determine their relative stabilities. The HOMO-LUMO gap analysis provides insight into dimers' electronic properties and relative reactivities. Furthermore, the analysis focuses on the changes in bond lengths, bond angles, and dihedral angles that occur upon complexation.

3.1. Relative Stabilities of the Dimers

We examine both their electronic and corrected complexation energies to compare the relative stabilities of the Thym_Ment_1, Thym_Ment_2, and Thym_Ment_3 dimers. The values of the energies and dipole moment are presented in Table 1. The analysis of the electronic and corrected complexation energies of the Thymol/Menthol dimers reveals significant differences in their relative stabilities. Thym_Ment_1 is the most stable one. This stability is primarily due to the strong O-H...O hydrogen bonding. This bond in the red dotted line equals 1.897 Å (Figure 1). Recall that our dimer is calculated in the isolated state. Abranches & col. calculate it in liquid medium at 1.710 Å, adopting a DFT with the B-P86 functional, a def-TZVP basis set and the COSMO solvation model [9].

Table 1. Electric and Energetic Properties of the Thym_Ment Dimers.

Dimer	Dipole Moment (Debye)	Polarizability (α) (Kcal/mol)	Relative Energy (kcal/mol)	Corrected Complexation Energy (kcal/mol)	Gap (eV)
Thym_Ment_1	3.23	138,853.4	0.0	-10.4	5.840
Thym_Ment_2	2.79	134,284.5	5.0	-7.4	5.944
Thym_Ment_3	2.64	134,151.5	8.5	-7.3	5.963

In contrast, Thym_Ment_2 and Thym_Ment_3 (Figure 2), which involve weaker π -H interactions between the menthol monomer's O-H bond and the thymol monomer's aromatic ring, are less stable. Their higher electronic and less negative complexation energies reflect the reduced interaction strength in these dimers. The slight differences in the complexation energies between Thym_Ment_2 and Thym_Ment_3 suggest that the orientation of the O-H bond relative to the aromatic ring has a minor effect on stability. On the other hand, the influence of the hydroxyl/hydroxyl interaction, which gave rise to the H bond, is much more significant in the Thym_Ment_1 dimer (Table 1).

3.2. Relative Reactivity of the Thym_Ment Dimers

The frontier orbitals of a given system, HOMO and LUMO, give an idea of the behaviour of other species. The frontier orbital gap allows us to qualify the system's kinetic stability and chemical reactivity. A small frontier orbital gap means it is more polarizable. It is usually combined with low kinetic stability and high chemical reactivity [10]. It is noted that the values of the energy gap vary in the same direction as those of relative energies. The lowest value is associated with the dimer Thym_Ment_1, hence its low kinetic stability and high chemical reactivity compared to the other two. Our results agree since the essential values of dipole moment and polarizability (α) are also associated with the dimer Thym_Ment_1. These frontier orbitals are shown in Figure 1 (Table 1).

3.3. Structural Analysis of the Thym_Ment Dimers

The structural parameters of the Thym_Ment_1 (Figure 1) dimer were carefully analyzed to understand the effects of complexation on bond lengths, angles, and dihedral angles. Changes in these internal coordinates indicate the molecular interactions that stabilize the dimer. Table 2 summarizes the key geometric parameters before and after complexation.

Table 2. Key Internal Coordinates Before and After Complexation in the Thym_Ment_1 Dimer.

Parameter	Thymol		Menthol		New Interactions
	Before	After	Before	After	
O1-H25 (Å)	0.965	0.976	-	-	-
O26-H56 (Å)	-	-	0.968	0.968	-
O1...O26 (Å)	-	-	-	-	2.797
H25-O1-C6 (°)	109.5	113.9	-	-	-

H56-O26-C28 (°)	-	-	107.1	107.6	-
O1-H25...O26 (°)	-	-	-	-	152.2
C3-C6-O1-H25 (°)	6.0	12.2	-	-	-
C27-C28-O26-H56 (°)	-	-	-64.4	-67.7	-
C6-O1...O26-C28 (°)	-	-	-	-	-137.1
C6-O1-H25...O26 (°)	-	-	-	-	169.6

The formation of the Thym_Ment_1 dimer results in significant changes in the internal coordinates within the thymol and menthol monomers, contributing to the complex's overall stability. A slight elongation of the O1-H25 bond in thymol is observed due to the forming of a hydrogen bond with the menthol hydroxyl group. In contrast, the O26-H56 bond in menthol remained unchanged at 0.968 Å, suggesting that the interaction primarily affects the thymol monomer. The value of distance O1...O26 is 2.797 Å. It is typical for hydrogen bonds. It further confirms the formation of a stabilizing interaction between thymol and menthol. The newly formed angle O1-H25...O26 is 152.2°, which is close to the ideal angle for hydrogen bonding.

In addition to the bond lengths and angles, significant changes were observed in the dihedral angles. Newly formed dihedral angles C6-O1...O26-C28 (-137.1°) and C6-O1-H25...O26 (169.6°) provide insight into the spatial arrangement of thymol and menthol within the dimer. These angles suggest that the molecules are aligned in a way that maximizes hydrogen bonding while minimizing steric hindrance (Table 2).

In the Thym_Ment_2 and Thym_Ment_3 dimers, the menthol monomer is positioned so that its hydroxyl group interacts with the aromatic ring of thymol (Figure 4). Therefore, few internal coordinates are directly affected by this interaction and the changes are more subtle. Unlike the more pronounced changes observed in the Thym_Ment_1 dimer, the Thym_Ment_2, and Thym_Ment_3 dimers show subtler modifications in their internal coordinates. The O26-H56 bond length in menthol increased slightly from 0.968 Å before complexation to 0.970 Å in Thym_Ment_2 and 0.971 Å in Thym_Ment_3. This minor elongation suggests a weak interaction between the O-H bond of menthol and the π -electrons of the thymol aromatic ring (Table 3).

Table 3. Key internal coordinates Before and After Complexation in the Thym_Ment_2 and Thym_Ment_3 Dimers.

Parameter	Menthol Before	Thym_Ment_2	Thym_Ment_3
O26-H56 (Å)	0.968	0.970	0.971
H56-O26-C28 (°)	107.1	107.6	107.6
C27-C28-O26-H56 (°)	-64.4	-71.8	-61.9

4. Conclusions

This study investigated the molecular interactions between thymol and menthol forming dimers using Density Functional Theory (DFT) at the B3LYP/6-31G(d,p) level. The focus was on understanding the nature and strength of interactions within three different dimers. By performing optimization calculations and evaluating corrected complexation energies, we reached essential conclusions concerning stability and interactions in these dimers.

The Thym_Ment_1 dimer, characterized by a strong O-H...O-H hydrogen bond, has the most stable configuration and the lowest electronic and complexation energies. In contrast, the Thym_Ment_2 and Thym_Ment_3 dimers, where the O-H group of menthol interacted with the aromatic ring of thymol, were less stable with higher electronic and complexation energies. Although significant, the interaction in these dimers resulted in a weaker stabilizing effect compared to Thym_Ment_1.

Our study aims to understand the probable interactions between the thymol molecule and that of menthol. The strong hydrogen binding capacity of thymol and menthol, particularly in configurations like Thym_Ment_1, and the good stability of dimers suggest that their union gives systems combining their mutual properties. Overall, this research provides useful information on the molecular interactions between thymol and menthol that will contribute to understanding their behaviour in reaction environments.

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