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A Density Functional Theory Study on the Role of Electronic Properties in the Antioxidant Activity of the Ajoene Molecule

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A Density Functional Theory Study on the Role of Electronic Properties in the Antioxidant Activity of the Ajoene Molecule[#]

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Abstract

The ajoene molecule is the main compound extracted of the garlic and besides its potential antioxidant activity it also presents several other biological properties such as to lower blood pressure and cholesterol, fight infections and prevent cancer. In this work we used the density functional theory (DFT) method with the aim to calculate some electronic molecular properties of the ajoene molecule and correlate them with its potential antioxidant activity. From the results obtained in this work, we verified that the *E*-ajoene (the *trans* structure) is more stable than the *Z*-ajoene (the *cis* structure), has a high electron-accepting character and a great probability of interacting with the biological receptor through a charge transfer mechanism.

Keywords. Ajoene; molecular mechanics; density functional theory; DFT.

1 INTRODUCTION

Throughout history, plant-derived substances have been used to induce healing, pleasurable feelings and as poisons to kill or incapacitate. It was not until the second half of this century that the specificity of such effects has been attributed to the involvement of specific cellular receptors [1]. Garlic has about 5000 years of folk medicine history. It has been reported the therapeutic effect of garlic on the circulatory system offering protection against stroke, coronary thrombosis and atherosclerosis. The active constituents are sulfur-containing compounds that are rapidly absorbed and metabolized. The principal medicinal uses of garlic are to lower blood pressure and cholesterol, fight infections and prevent cancer [2].

Several compounds are involved in the possible effects anticancer provided by garlic. The sulfur-containing compounds, which occur naturally in garlic and onions, make cells vulnerable to

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ajoene molecule [2]. The calculated molecular properties obtained for the neutral and positively and negatively charged species of ajoene were: total energy (E_T), energy of the highest occupied molecular orbital (E_{HOMO}), energy of the lowest unoccupied molecular orbital (E_{LUMO}), energy of the semi-occupied molecular orbital (E_{SOMO}), atomic charges and absorption spectra.

2.2 Computer Software

2.2.1 Quantum chemistry software

The structure of both isomers of the ajoene molecule was modeled using the molecular mechanics method MM+ [4,5] for a pre-optimization, followed by a conformational analysis performed by the CHEMPLUS program [6]. Afterwards, the Density Functional Theory (DFT) with the B3LYP functional (DFT/B3LYP) [7,8], as implemented in the molecular package GAUSSIAN 98 [9], was used for a final optimization of the two isomers (*cis* and *trans*). The DFT/B3LYP calculations for the neutral and positively charged ajoene species were performed with the 6-311G* basis set. For the negatively charged ajoene specie, the diffuse 6-311+G basis set was used, as a diffuse orbital appears when we have a negative ion.

The theoretical spectra of ajoene were obtained with the ZINDO method [10], as implemented in the molecular package CERIUSt² [11]. The ZINDO method provides a graphical view of the theoretical spectra and is one of the most used methods to perform molecular calculations of absorption energies, as it was calibrated to give accurate results for a large series of molecular systems [12].

3 RESULTS AND DISCUSSION

The chemical structure of the two isomers (*cis* and *trans*) of the ajoene molecule are displayed in Figure 2. In fact, the two structures (*cis* and *trans*) differ only in the torsion angle formed by the atoms C₅–C₆–C₇–S₈, according to the numbering system shown in Figure 1.

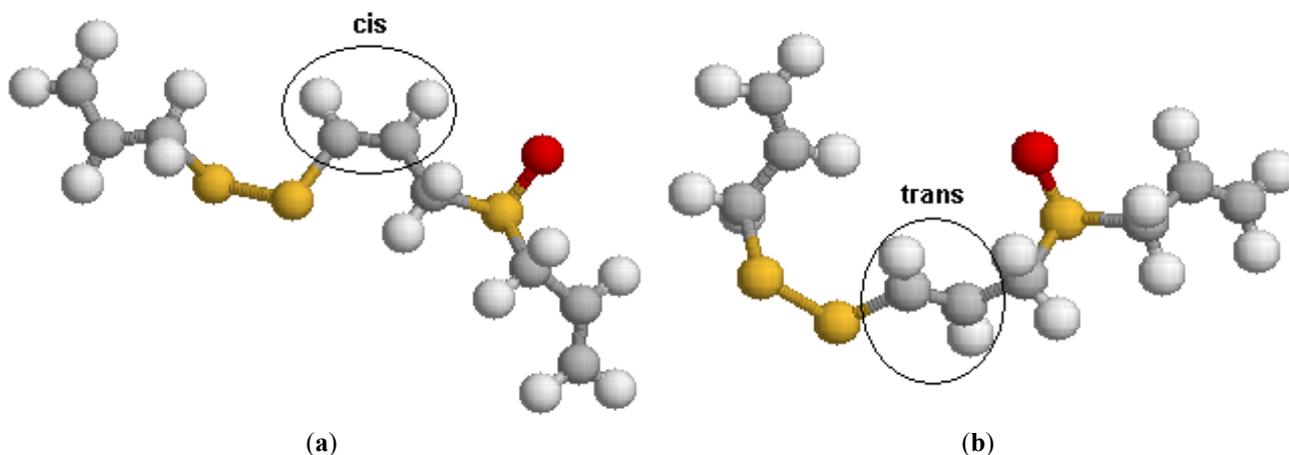


Figure 2. Optimized structures of the two ajoene isomers obtained with the DFT method: (a) *Z*-ajoene (*cis*) and (b) *E*-ajoene (*trans*).

In order to verify the chemical stability of the *cis* and *trans* isomers, it was necessary to calculate the total energy (E_T) for these isomers of the ajoene molecule (see Table 1). From Table 1 we can see that the *E*-ajoene molecule presents a lower value for E_T than the *Z*-ajoene, indicating that the *trans* structure (*E*-ajoene) is more stable than the *cis* one (*Z*-ajoene). Here it is interesting to mention that S. Erkoç *et al.* [2], working with the semi-empirical method AM1, found that both ajoene isomers (the *cis* and *trans* structures) have the same geometry after their AM1 optimization. Now in our study we have found, through another optimization methodology, that the *trans* ajoene structure is the most stable one.

Table 1. Some electronic properties calculated for the ajoene species *cis* (*E*-ajoene) and *trans* (*Z*-ajoene). In parentheses are indicated the molecular charges used (0, -1 and +1)

	<i>Z</i> -ajoene (0)	<i>E</i> -ajoene (0)	<i>E</i> -ajoene (-1)	<i>E</i> -ajoene (+1)
	DFT/B3LYP method			
E_T (au)	-1621.2224593	-1621.22394669	-1620.94600010	-1620.92657674
E_{HOMO} (au)	-0.22694	-0.22498	-0.04515	-0.37899
E_{LUMO} (au)	-0.04657	-0.03624	0.08627	-0.23015
E_{SOMO} (au)	–	–	0.03810	-0.36024

Due to the supposed antioxidant activity presented by the ajoene [2], we decided to perform DFT/B3LYP calculations with the *E*-ajoene specie (the most stable structure) with charges +1 and -1 with the aim to investigate the electron-donating and electron-accepting character of the ajoene molecule. Comparing the obtained E_T values showed in Table 1 for *E*-ajoene (-1), we can see that *E*-ajoene (-1) has lower E_T value than *E*-ajoene (+1), indicating that the *E*-ajoene molecule has a great tendency to receive electrons in a charge transfer reaction.

The calculated E_{LUMO} value displayed in Table 1 for the neutral *E*-ajoene specie (*E*-ajoene (0)) is an indicative that the ajoene molecule has a high electron-accepting character. In fact the smaller the E_{LUMO} value, the greater the electron-accepting character of a compound [12]; and according to a previous work [13], that classifies biomolecules as electron donors or electron acceptors taking into account their calculated E_{LUMO} values, the *E*-ajoene molecule has a high electron-accepting character and this means that this molecule probably interacts with the biological receptor through a charge transfer mechanism. Thus, it would be also interesting to look at the charge variations when an electron is added to the neutral ajoene specie. Table 2 displays the charge variation between the neutral (*E*-ajoene (0)) and negatively single-ionized (*E*-ajoene (-1)) ajoene species. From Table 2 we can see that the biggest charge variations occur exactly on the atoms C₆, S₈, S₉ and C₁₁; thus the most favorable sites where a charge transfer can occur are located on the atoms C₆, S₈, S₉ and C₁₁.

Also from Table 2 (first column) we can notice that the hydrogen atoms bonded to the unsaturated carbon atoms (C₁ and C₂, C₆ and C₇ and C₁₁ and C₁₂), i.e. H₁₄, H₁₅, H₁₆, H₂₁, H₂₂, H₂₅, H₂₆ and H₂₇, have the largest excess of positive charge (greater than + 0.12), indicating that these hydrogen atoms can be expected to leave the ajoene molecule first in a possible proton transfer reaction (a proton transfer mechanism can be also related to the antioxidant activity of molecules).

Table 2. Atomic charges calculated with the DFT method for the neutral and negatively charged *E*-ajoene molecule

Atoms	Charge = 0	Charge = -1
1 C	-0.069	-0.025
2 C	-0.385	-0.472
3 C	0.094	0.083
4 S	0.166	0.012
5 C	0.167	0.713
6 C	-0.176	-0.597
7 C	-0.046	0.136
8 S	-0.071	-0.340
9 S	-0.212	-0.408
10 C	0.348	0.900
11 C	-0.123	-0.294
12 C	-0.405	-0.418
13 O	-0.479	-0.482
14 H	0.149	–
15 H	0.153	–
16 H	0.132	–
17 H	0.046	–
18 H	0.036	–
19 H	-0.017	–
20 H	0.031	–
21 H	0.122	–
22 H	0.129	–
23 H	-0.051	–
24 H	0.016	–
25 H	0.129	–
26 H	0.161	–
27 H	0.158	–

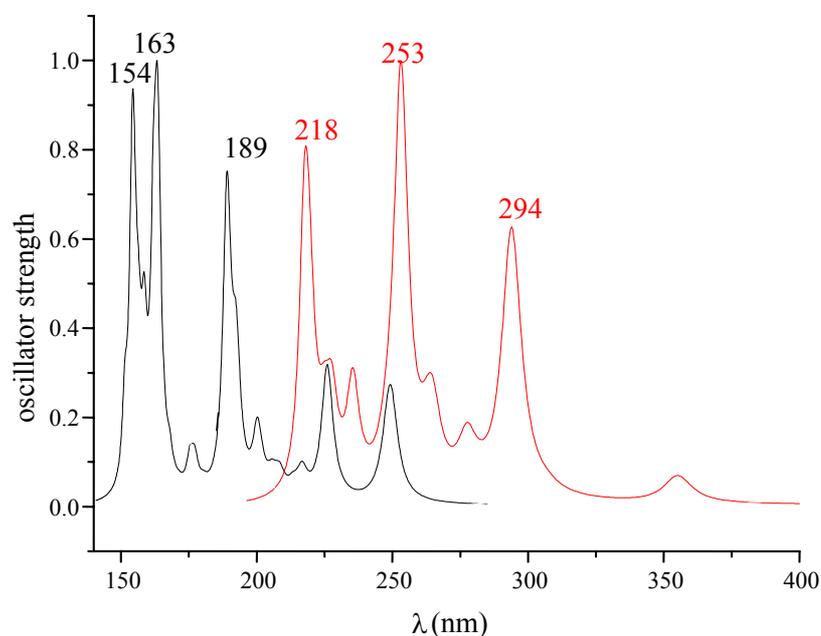


Figure 3. Absorption spectra calculated with the ZINDO method for the *E*-ajoene molecule with charge = 0 (black line) and -1 (red line).

In the work of Erkoç *et al.* [2], they also analyzed the hydrogen charges (using the AM1 method), but they found that only the hydrogen atoms H₂₁ and H₂₂ had the largest excess of positive charge. However, our DFT calculations showed that not only the hydrogen atoms bonded to the central double bonded carbon atoms (*i.e.* H₂₁ and H₂₂) are the ones with the largest excess of positive charge, but in fact all the hydrogen atoms bonded to the unsaturated carbon atoms in the ajoene molecule have an excess of positive charge.

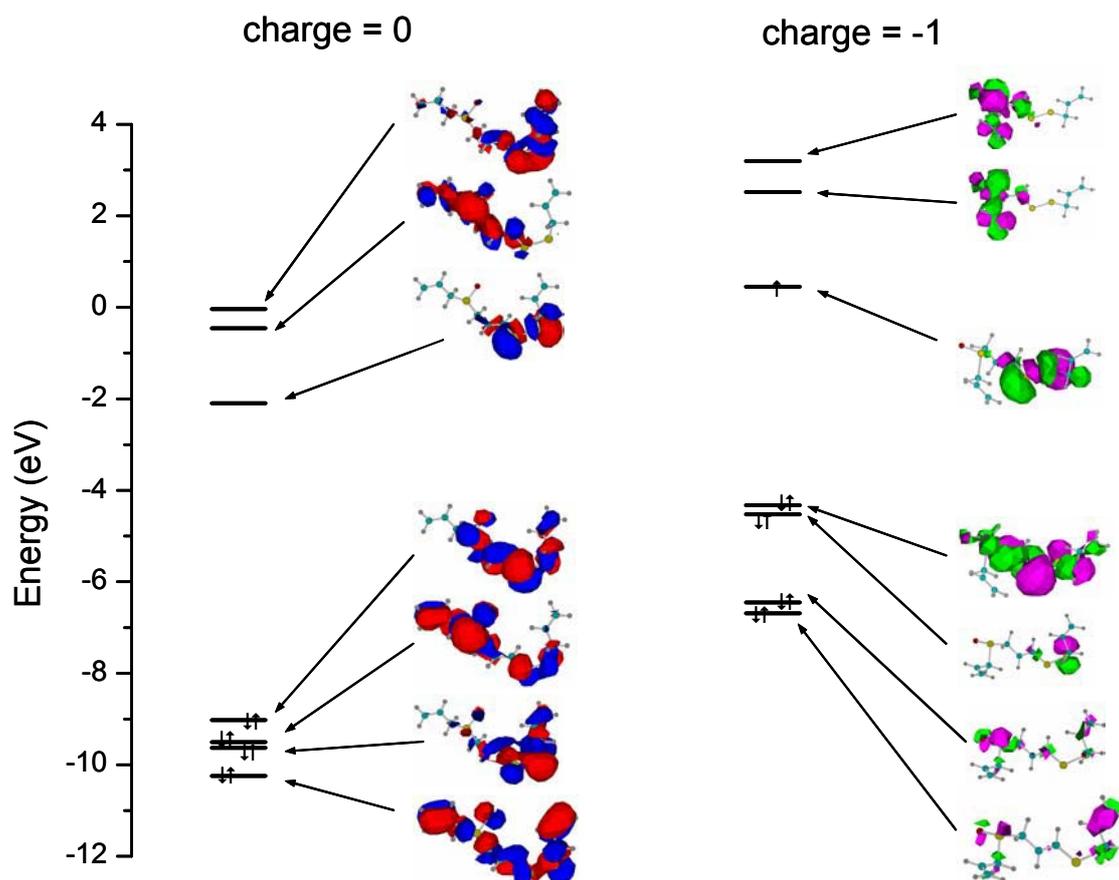


Figure 4. The energy diagram of the molecular orbitals involved in the main transitions of the absorption spectra of the neutral and negatively charged *E*-ajoene molecule.

Table 3. The main bands of the neutral and negatively charged *E*-ajoene molecule (λ_{\max} , in nm) and the corresponding transitions

Isomer	λ_{\max}	Transition
<i>E</i> -ajoene (0)	154	HOMO-3→LUMO+1
	163	HOMO-1→LUMO+2
	189	HOMO-1→LUMO
<i>E</i> -ajoene (-1)	218	HOMO→SOMO and HOMO→LUMO+4
	253	HOMO-1→LUMO+1
	294	HOMO→SOMO

As our DFT calculations showed that the ajoene molecule has a high electron-accepting character, we decided to study the electronic (absorption) spectrum for the neutral and negatively

charged *E*-ajoene species. The absorption spectra calculated with the ZINDO method are presented in Figure 3. Table 3 presents the main absorption bands and the corresponding transitions. The theoretical spectra of the two species show that there are no absorption bands in the visible region, but the negatively charged molecule presents the absorption maximum (253 nm) shifted to greater wavelengths, differently from that obtained for the neutral molecule (163 nm).

Also, an analysis of the molecular orbitals involved in the main transitions of these two species (the neutral and negatively charged molecules) was performed, and these orbitals are represented in Figure 4 by an energy diagram. The charged molecule presents molecular orbitals with higher energy values and a semi-occupied molecular orbital (SOMO). Table 3 shows the wavelength in which the transitions related to these orbitals occur. The most intense bands in the spectra are 163 nm for the neutral molecule and 253 nm for the charged one. Both correspond to an electronic excitation that transfers the electron from one side to the other side of the molecule (see Table 3 and Figure 4).

4 CONCLUSIONS

In this work we have showed by DFT calculations that the *E*-ajoene (the *trans* structure) is the most stable conformation adopted by the ajoene molecule. The calculated E_{LUMO} values showed that the *E*-ajoene molecule has a high electron-accepting character, which can be related to its potential antioxidant activity, and also indicates that this molecule probably interacts with the biological receptor through a charge transfer mechanism.

From the calculated atomic charges for the neutral and negatively single-ionized ajoene species, we verified that the biggest charge variations occur exactly on the atoms C₆, S₈, S₉ and C₁₁, indicating that these atoms would be the probable sites where the charge transfer process would occur. The evaluation of the atomic charges on the hydrogen atoms of the ajoene molecule showed that the largest excess of positive charge are located on the hydrogen atoms bonded to the unsaturated carbon atoms of the molecule.

The theoretical spectra for the neutral and negatively charged *E*-ajoene molecules (obtained with the ZINDO method) presented no absorption bands in the visible region, but the negatively charged molecule presented the absorption maximum shifted to greater wavelengths, differently from that obtained for the neutral molecule.

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