
Investigation of the Excited States of Resveratrol and Related Molecules

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ABSTRACT: Resveratrol, a natural product derived from grapes, is a phytoalexin with antioxidative activity. In this work we present initial results of an ongoing study of the geometry of the ground state and of the first two (singlet and triplet) excited states of resveratrol and the structurally related compounds diethyl-stilbestrol-stilbene and *trans*-stilbene. The molecular geometries were optimized both at the semiempirical and ab initio (restricted Hartree-Fock/6-31G*) levels, and the corresponding absorption spectra were calculated using the intermediate neglect of differential overlap/spectroscopically parameterized with interaction of configurations (INDO/S-CI) methodology. © 2003 Wiley Periodicals, Inc. *Int J Quantum Chem* 95: 213–218, 2003

Key words: ab initio method; resveratrol; semiempirical/CI methods; theoretical absorption spectra; *trans*-stilbene

Introduction

Interest in the properties of the resveratrol molecule has been spurred by the need of explaining the so-called “French paradox.” This corresponds to the controversy about epidemiological data indicating that in France there is a lower morbidity through cardiovascular and coronary diseases than in other developed countries despite the fact that the French consume a diet that is fairly high in fat [1]. An invoked explanation for the paradox is that in France the consumption of red

wine above the world average could have a particular protective effect due to the presence of resveratrol in the skin of certain types of grapes [2].

In fact, some studies recently suggested that resveratrol is an effective antioxidant agent [3, 4]. Some authors [5, 6] pointed out that it is feasible to correlate molecular parameters (such as size, shape, and electronic properties) of organic compounds to their biological selectivity. Even so, and in spite of the many experimental studies that so far have been done on resveratrol properties, it is not clear which of its molecular features would be responsible for its antioxidative activity. As a stilbenoid molecule, *trans*-resveratrol (TR) consists of two phenyl rings connected through a nonsaturated bridge; three hydroxyl groups are substituted on the phenyl rings [see Fig. 1(a), where the numbers 15, 16, and 17

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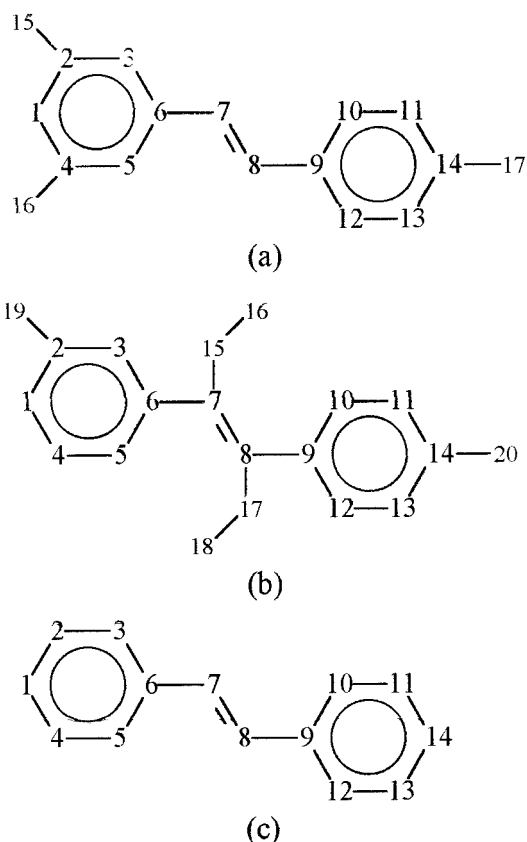


FIGURE 1. Schematic structure of the molecules investigated: (a) TR, (b) DSS, and (c) TS.

have been assigned to the oxygen atoms], and its chemical structure resembles that of diethylstilbestrol-stilbene (DSS), a synthetic estrogen that has a definite physiological activity [Fig. 1(b), where the numbers 15, 16, and 17 have been assigned to the oxygen atoms]. The structural similarity between phenolic compounds found in red wine and estrogens has already led to preliminary investigations of their physiological activity [7]. Recently [8], we used semiempirical methods to compare the charge distribution and the theoretical absorption spectra of these two molecules to those of *trans*-stilbene (TS), the benchmark compound for fluorescence and photoisomerization studies in stilbenes [Fig. 1(c)] [9].

It is well known that the nature of the substituent groups can affect the excited state isomerization mechanism of stilbenes [10]. In this work we present semiempirical and *ab initio* results for the electronic and structural properties of TS, TR, and DSS. We analyze the bond length distributions for the ground state and for the two lowest-lying ex-

cited (singlet and triplet) states. We also compare the semiempirical and *ab initio* simulated absorption spectra of these three molecules.

Methodology

The reactivity of biological molecules is in part affected by the electrostatic fields generated in the process of charge transfer [11], which are strongly determined by geometrical factors. Unfortunately, experimental geometric data are still not available for resveratrol, and hence we resort to geometry optimization to obtain the relevant information.

The geometry of each one of the three structures depicted in Figure 1 was completely optimized using parametric method 3 [12] with configuration interaction (PM3/CI). All the PM3/CI calculations were carried out with the MOPAC program [13]. For the *ab initio* calculations we have used the Gaussian 94 [14] package and the corresponding geometries were optimized with the standard restricted Hartree-Fock (RHF)/6-31G* basis set. Once the optimized geometries were determined, both at the semiempirical and *ab initio* levels, the corresponding absorption spectrum was calculated using the INDO/S-CI (intermediate neglect of differential overlap/spectroscopic-configuration interaction) included in the ZINDO program [15–20], with parameters chosen to give the best description of the UV-visible optical transitions [21–26]. Approximately 200 configurations were investigated for each molecule, including single and double excitations.

Results and Discussion

Although the photoisomerization characteristics of substituted stilbenes are extremely dependent on the excited-state geometries [9], the competition between fluorescence and vibrational relaxations is determined by the induced charge rearrangements [10]. Theoretical studies of the optical properties of TS have already pointed out that subtle variations of the π -conjugation may have strong influence upon the outer valence levels [27]. Then, for each of the molecules considered, we have calculated the variation of the bond length distribution between the ground state (a singlet) and the first singlet excited state and between the ground state and the lowest triplet excited state. In general terms, important differences in the electronic structure of the TS,

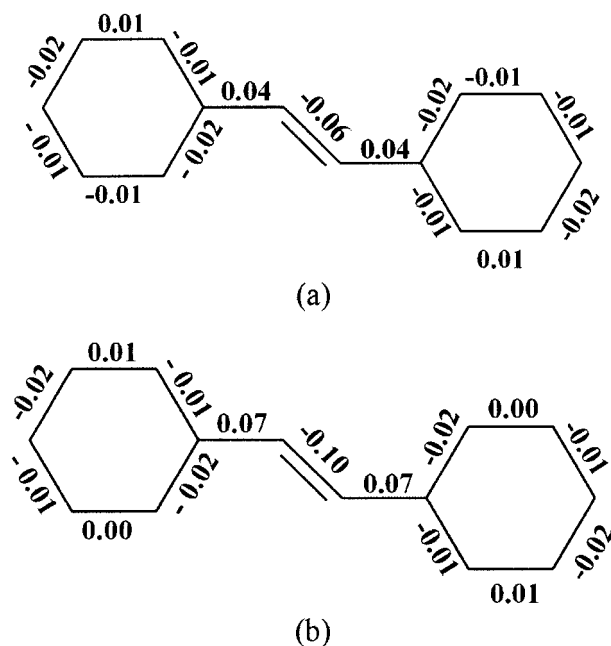


FIGURE 2. The PM3/CI calculated variation of the bond length distribution between the (a) ground state and the first singlet excited state and the (b) ground state and the first triplet excited state of TS molecule. (Positive values mean decrease upon excitation).

TR, and DSS molecules seem to occur in the carbon atoms of the polyenic bridge connecting the two phenyl rings [8], as the degree of loss of double-bond character of the central ethylenic moiety is determinant for the isomerization dynamics of the compound [9].

Accordingly, we have found that the most noticeable differences in the bond length distributions of TS molecule (Fig. 2) resulting from the excitation are localized in the conjugated bridge (i.e., atoms 6, 7, 8, and 9) between the phenyl rings: in general terms, because in the excited states the length of the double bonds increase and that of the single bonds decrease, upon excitation there is a tendency to the bridge to become less conjugate in character.

For the TR molecule, on the other hand, the changes in bond length are a little more widespread along the molecular structure, involving not only the conjugated bridge but also some other specific bonds (Fig. 3). The same tendency for a less conjugated bridge is observed, but by far the most dramatic change is seen for the CO bond 14–17 upon excitation to the first triplet excited state: as calculated in Ref. [8], this reduction in bond length is accompanied by an intense separation of charges in atoms 14 and 17, leading to a more electron-defi-

cient carbon atom. Also note the peculiar behavior of the changes in the bond lengths between atoms 3–2 and 5–4, which occur in opposite directions.

As for the DSS molecule, the changes are almost entirely confined to the bond lengths in the conjugated segment comprising atoms 15, 7, 8, 9, and 12, with a peculiar conformational distortion of the *para*-substituted phenyl ring (Fig. 4). At the same time, an important reorganization of the geometry of this molecule occurs in the spatial arrangement of the bridge connecting the rings. Upon geometry optimization from an initial planar configuration, the molecule suffers a torsionlike motion that brings the two phenyl rings, respectively, above and below the original molecular plane while remaining parallel to each other. At the final conformation, the central double bond of the polyenic bridge and the attached ethyl groups are disposed in a perpendicular position relative to the cyclic rings. Although this peculiar behavior is seen for all optimized geometries considered (ground state and the two first excited states), we have found that the value of the dipole moment of the singlet excited state is unusually large, being at least one order of magnitude bigger than those of the lowest triplet

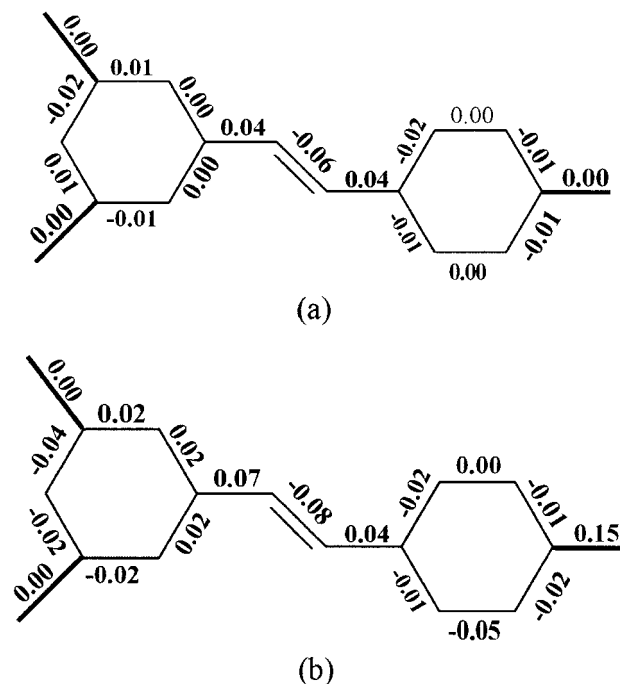


FIGURE 3. The PM3/CI calculated variation of the bond length distribution between the (a) ground state and the first singlet excited state and the (b) ground state and the first triplet excited state of TR molecule. (Positive values indicate an increase upon excitation).

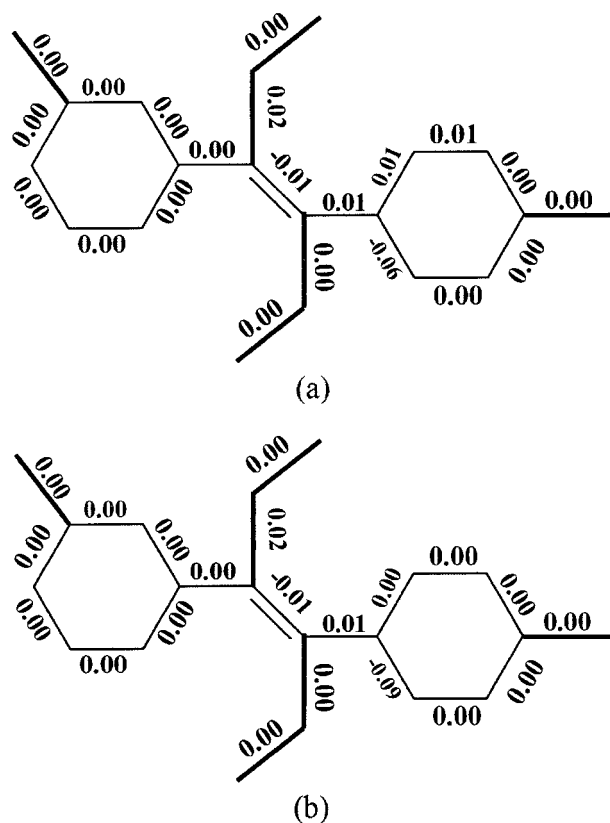


FIGURE 4. The PM3/CI calculated variation of the bond length distribution between the (a) ground state and the first singlet excited state and the (b) ground state and the first triplet excited state of *trans*-DSS molecule. (Positive values indicate an increase upon excitation).

excited state or of the ground state. As pointed out in our previous work [8], intense asymmetric charge reorganization is observed to accompany the excitation of the DSS molecule, especially to the first excited singlet state.

Finally, we have utilized the INDO/S-CI approach to simulate the absorption spectrum of the TS, TR, and DSS molecules (Fig. 5) considering the fully optimized 6-31G* geometries. Although the optical properties of TS have been extensively studied both at the theoretical [27, 28] and experimental [9, 29] levels, the TR and DSS molecules have been much less investigated. For the former, UV [30] and fluorescence [31] spectra became recently available. We have also compared the current results to the pure semiempirical spectra (i.e., those calculated using PM3/CI geometries) discussed in our previous work [8]. The most important transitions identified in the INDO/S-CI absorption spectra for the

ab initio RHF/6-31G* geometries are presented in Table I, where H and L represent the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).

When the ab initio 6-31G* geometry of TS is considered [Fig. 5(a), top], the lower energy band in the absorption spectrum is shifted from 300 nm to 276 nm, its oscillator strength (o.s.) is decreased (0.67, compared with a value of 0.99, obtained in the pure semiempirical calculation) but it still remains mainly a $|H \rightarrow L\rangle$ transition. Note that for the ab initio geometry the calculated spectrum is better resolved, with the splitting of the high-energy band.

For the TR molecule, we also find that the lowest RHF/6-31G* energy band [Fig. 5(b), top] is blue-shifted (from 304 nm to 283 nm) and has the o.s. reduced to 1.03 but remains essentially a $|H \rightarrow L\rangle$ transition. The large band centered at ≈ 178 nm, seen in the spectrum corresponding to the semiem-

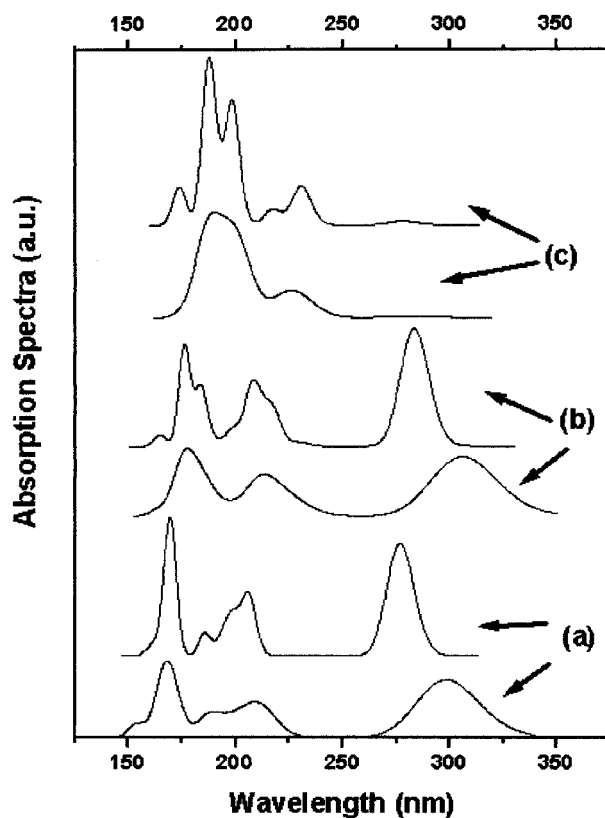


FIGURE 5. The INDO/S-CI theoretical absorption spectra spectrum for TS (a), TR (b), and DSS (c) molecules, calculated using the PM3 (lower curve in each case) and RHF/6-31G* (upper curve) optimized geometry.

TABLE I
Principal INDO/S-CI UV-Vis absorption transitions as determined from calculations based on optimized ground-state 6-31G* geometries, with corresponding oscillator strengths (o.s.).^a

Molecule	nm	o.s.	Absorption
TS	276	0.67	0.95 H → L>
	204	0.64	0.64 H-1 → L> -0.62 H → L + 1>
	186	0.13	0.49 H-1 → L>
	170	0.47	0.55 H-3 → L + 3> -0.50 H-2 → L + 3>
			0.90 H → L>
TR	283	1.03	0.60 H-2 → L> -0.47 H → L + 2>
	205	0.45	-0.45 H-4 → L + 1> 0.40 H-2 → L + 2> 0.39 H-2 → L + 4>
	176	0.67	0.70 H → L> -0.56 H-4 → L + 3>
			-0.62 H-1 → L + 2> -0.28 H-2 → L + 3>
DSS	278	0.03	0.56 H-4 → L + 3> 0.36 H-3 → L + 2>
	230	0.12	-0.47 H-1 → L + 4> 0.40 H-3 → L + 2>
	200	0.27	0.37 H-5 → L + 4> -0.35 H-4 → L + 5>
	185	0.30	
	173	0.16	

^a Note that although in the TR case the most important transition is a HOMO-LUMO excitation, those involving neighboring occupied and unoccupied orbitals have a more important contribution to the TS and (especially) DSS spectra.

pirical geometry is split in the ab initio result (see Table I).

No blue shifts in the ab initio spectrum are found for the DSS molecule [Fig. 5(c), top]. The low energy band occurs at 278 nm, its o.s. is equal to 0.03, and it corresponds to a mixing of the |H→L> and |H-4→L+3> transitions. The bands between 180 nm and 200 nm, composed by a mixing of |H-1→L+4>, |H-3→L+2> and |H-4→L+3> transitions, are the most important.

From the analysis of the calculated spectra, we once again find that, although the |H→L> transition is dominant for the TS and TR molecules, this is not the case for the DSS molecule.

Summary

As part of a long-term project of investigation of the electronic properties of stilbenoid molecules, we

have presented a comparative study of the geometry and theoretical spectrum of resveratrol (a molecule whose attributed antioxidative activity has been linked to the preventive treatment of heart diseases [32] and human cancer) to the structurally related compounds DSS and TS. The latter has been more extensively investigated both at the theoretical and at the experimental level than have the others.

The geometries at the ground state and at the first singlet and first triplet excited states were optimized both at the semiempirical and ab initio (RHF/6-31G*) levels. The absorption spectrum of each molecule was calculated using the INDO/S-CI methodology and compare favorably with the results available in the literature. The study of the charge distribution and charge polarization processes in organic molecules is a key step for the identification of the possible form-function relationships. The antioxidative activity of resveratrol would be amenable to suitable chemical modifications by appropriate change of the density of charge in specific sites. The qualitative information gathered in this work about the electronic structure and absorption spectrum of these molecules gives us better directions for further theoretical and experimental investigations now in progress.

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