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Quantum chemistry calculation of resveratrol and related stilbenes

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Abstract

We report a semiempirical investigation of the first excited states and of the spectroscopic properties of resveratrol, a phytoalexin with well-known antioxidative properties, and of structurally related stilbenes. The analysis of the calculated bond length and charge rearrangements resulting from the photoexcitation and of the corresponding theoretical spectra gives us some insight of how chemical modifications of these molecules could affect the possible physiological properties of resveratrol.

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1. Introduction

It has been recently suggested that, due to the presence of the resveratrol molecule in the skin of certain types of grapes, consume of red wine could have a particular protective effect against cardiovascular diseases [1,2]. In fact, some studies have suggested that resveratrol is an effective antioxidant agent [3,4]. Although it is possible [5,6] to correlate molecular parameters (such as size, shape and electronic properties) of a given compound to its biological activity, it remains not clear to this moment the details of the antioxidative properties of resveratrol. The resveratrol molecule (Fig. 1) is

composed by two phenyl rings connected through a nonsaturated carbon bridge with 3 OH groups substituted on the phenyl rings. It is well known [7] that the interaction of biological molecules can be strongly dependent on the electrostatic fields generated in the process of charge transfer, and those fields are mainly determined by geometrical factors [8,9]. Since experimental conformation data are not available for resveratrol, we will have to rely on theoretical information gathered from geometry optimization.

As it can be seen in Fig. 1, *trans*-resveratrol (TR) has a chemical structure similar both to diethyl-stilbestrol-stilbene (DSS), a synthetic estrogen and to *trans*-stilbene (TS), a conjugated molecule that serves as standard for comparison of fluorescence and photoexcitation studies in stilbenes. In this work we present a semiempirical (including configuration interaction contributions)

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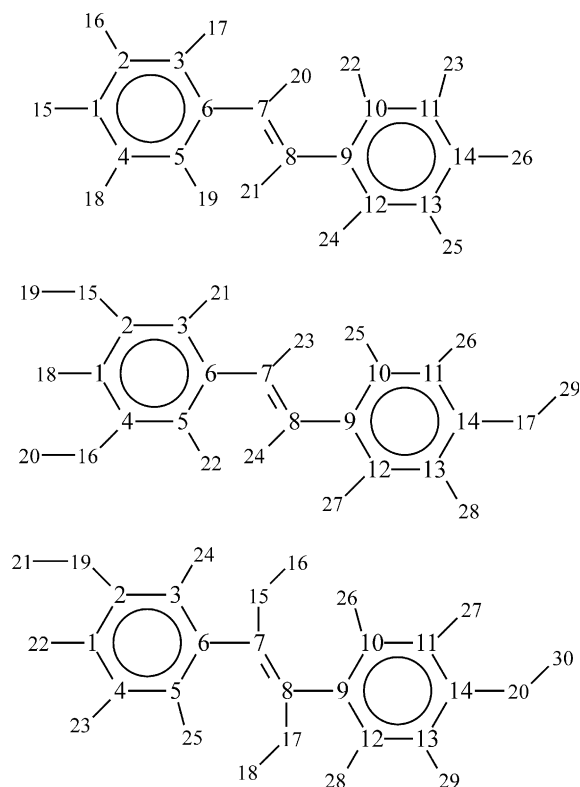


Fig. 1. Schematic chemical structure of the *trans*-stilbene (TS, top), *trans*-resveratrol (TR, middle part) and *trans*-diethylstilbestrol-stilbene (DSS, bottom) molecules, respectively. Note: In the TR [DSS] molecule, the oxygen atoms have been assigned numbers 15, 16 and 17 [16,18–20].

investigation of the electronic and structural properties of TS, TR and DSS. We have analyzed the bond length and charge distributions for the ground and low-lying excited (singlet and triplet) states and computed the theoretical absorption and emission (fluorescence and phosphorescence) spectra of these molecules.

2. Methodology

For each of the structures of Fig. 1, the geometry was completely optimized using the Parametric Method 3 [10] with configuration interaction (PM3/CI). All the PM3/CI calculations were carried out with the MOPAC program [11]. Once the optimized geometry was determined, the absorption

spectrum of each molecule was calculated using the intermediate neglect of differential overlap/configuration interaction (INDO/S-CI) [12–18], with parameters chosen to give the best description of the UV–VIS optical transitions [19–22]. Approximately 200 configurations were investigated for each molecule, including singlet and doublet states. For obtaining the fluorescence and phosphorescence spectra we have modified the ZINDO package by considering the geometry of the first excited states (singlet and triplet, respectively) in the description of the emission process. (We will refer to this approach as a DNdM-INDO/S-CI calculation.) In this calculation, we have taken into account from the first 9-UMOs (unoccupied molecular orbitals) to the last 9-OMOs (occupied molecular orbitals) and adopted the Mataga-Nishimoto γ .

To better understand the electronic charge redistribution (and consequent conformational change) which must accompany the excitation process, we have compared the molecular structure and the distribution of electronic charge of the optimized ground state of each molecule to those corresponding to the optimized lowest singlet and the lowest triplet excited configurations.

3. Results and discussion

We present the net charge distributions for the ground state (a singlet) and the lowest singlet and triplet excited states of the TS, TR and DSS molecules in Figs. 2–4, respectively. As it could be expected from simple chemical intuition, for all three molecules the most noticeable differences seem to be concentrated in the carbon atoms of the backbone region between the phenyl rings.

While for TS (Fig. 2), a molecule with inversion symmetry, the overall net differences in the electronic charge distribution are relatively small, the same behavior is clearly not present in the TR molecule (Fig. 3); here, there is a more pronounced charge variation, mainly over the doubly substituted phenyl ring. It is worthwhile to point out that while the oxygen atoms 15 and 16 do not suffer noticeable charge variation, there is a decrease in charge for oxygen 17 in both excited

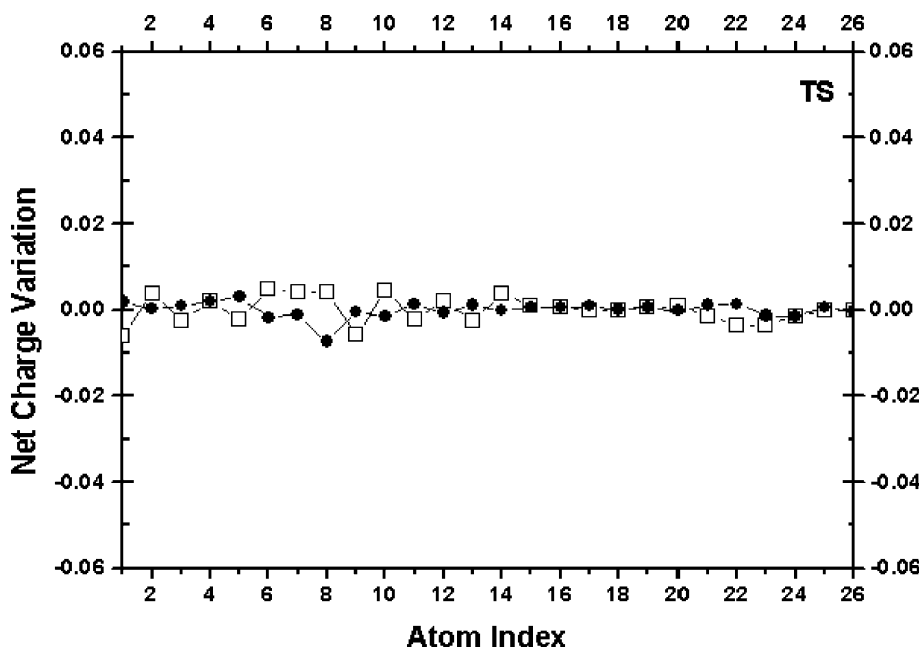


Fig. 2. PM3/CI calculated net differences in the electronic charge distributions between (□) the ground state and the first singlet excited state and (●) the ground state and the first triplet excited state of *trans*-stilbene (TS) molecule. (Positive values mean decrease upon excitation.)

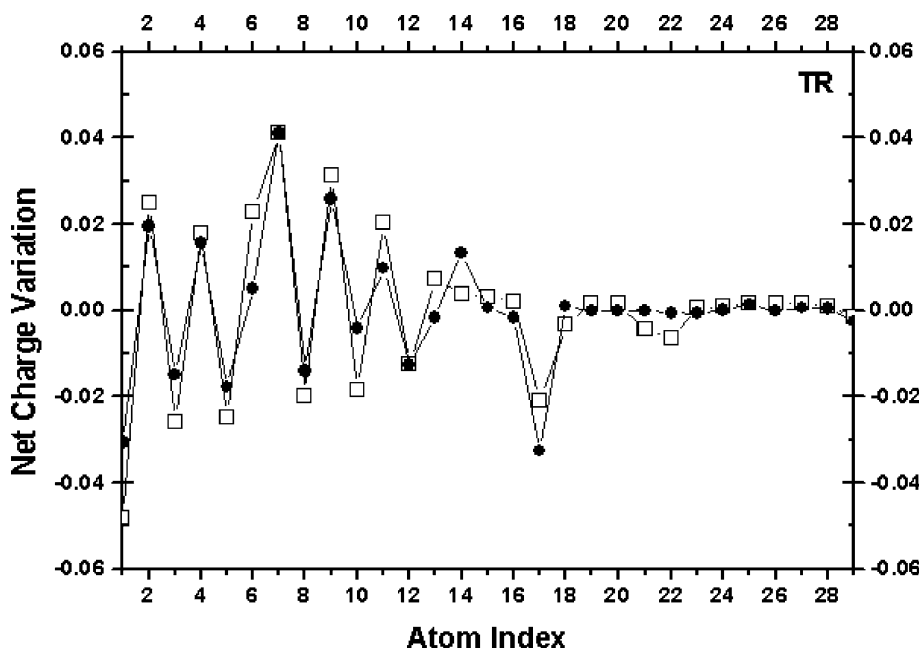


Fig. 3. PM3/CI calculated net differences in the electronic charge distributions between (□) the ground state and the first singlet excited state and the ground state and (●) the first triplet excited state of *trans*-resveratrol (TR) molecule using the PM3/CI method. (Positive values mean decrease upon excitation.)

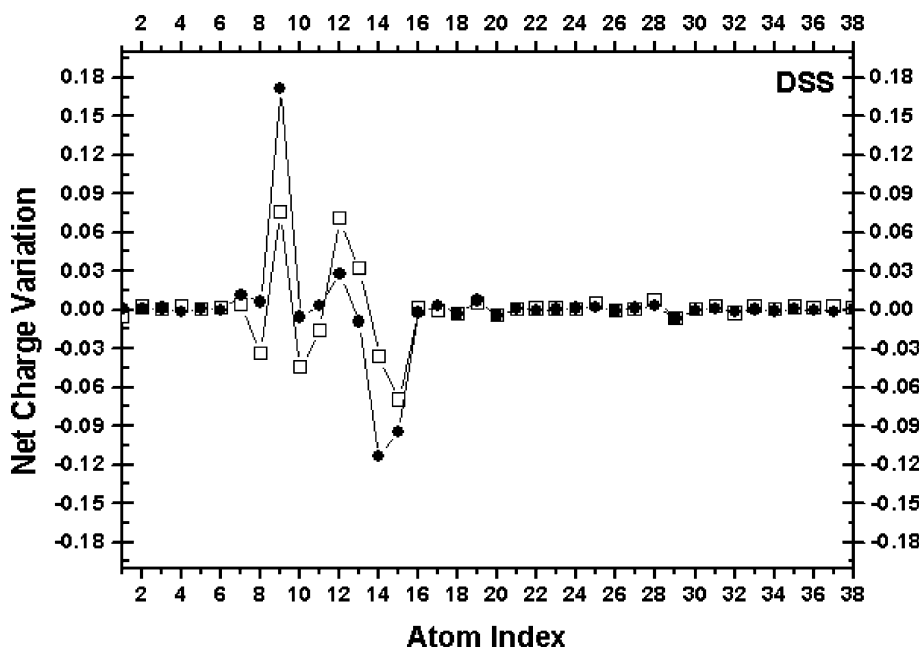


Fig. 4. PM3/CI calculated net differences in the electronic charge distributions between (□) the ground state and the first singlet excited state and (●) the ground state and the first triplet excited state of *trans*-diethyl-stilbestrol-stilbene (DSS) molecule using the PM3/CI method. (Positive values mean decrease upon excitation.)

states. Therefore, we see that contrary to what was observed in the TS molecule, upon excitation of TR there are definite charge rearrangement upon specific sites. These sites are then promising candidates to be involved in the physiological activity of the molecule, affecting its oxidative properties.

It is for the DSS molecule (Fig. 4), however, a stilbenoid compound with recognized pharmacological properties, that the most important differences in the net charge distribution can be identified. For instance, the intense asymmetric charge reorganization (specially for the first triplet excited state) involving atoms 9, 12, 14 and 15 is associated to an unusually large value of the corresponding dipole moment, which is one order of magnitude larger than those of the lowest triplet state and to the two lowest excited states of the TR molecule.

We have used the INDO/S-CI approach to simulate the absorption spectrum of the TS, TR and DSS molecules for the fully optimized PM3/CI (Fig. 5) geometries and interpret the main calculated transitions in Table 1. While for TS and TR

the first optical transition appears at 300 and 304 nm, respectively, and it is essentially a HOMO to LUMO ($|H \rightarrow L\rangle$) transition (with corresponding coefficients of 0.99 and 0.94, and oscillator strengths (o.s.) of 1.23 and 1.14), for the DSS molecule the first optical transition is predicted to happen at 282 nm and to be composed by a mixing of $0.46|H - 4 \rightarrow L + 3\rangle$, $0.64|H \rightarrow L\rangle$ and $-0.47|H - 1 \rightarrow L\rangle$ transitions with o.s. = 0.04. Note that for DSS the $\pi-\pi^*$ transition is in the same region as other competing transitions and has a smaller o.s. (=0.04) when compared with the corresponding optical gap transitions predicted for the TR and TS molecules.

We have carried out the DNdM-INDO/S-CI calculations to simulate the fluorescence and phosphorescence spectra of TS, TR and DSS molecules. These spectra were obtained by broadening each of these principal transitions by a suitably weighted Gaussian function normalized to the calculated oscillator strengths [19–22]. The results are also displayed in Fig. 5. While a significant Stokes shift is predicted in all cases, we

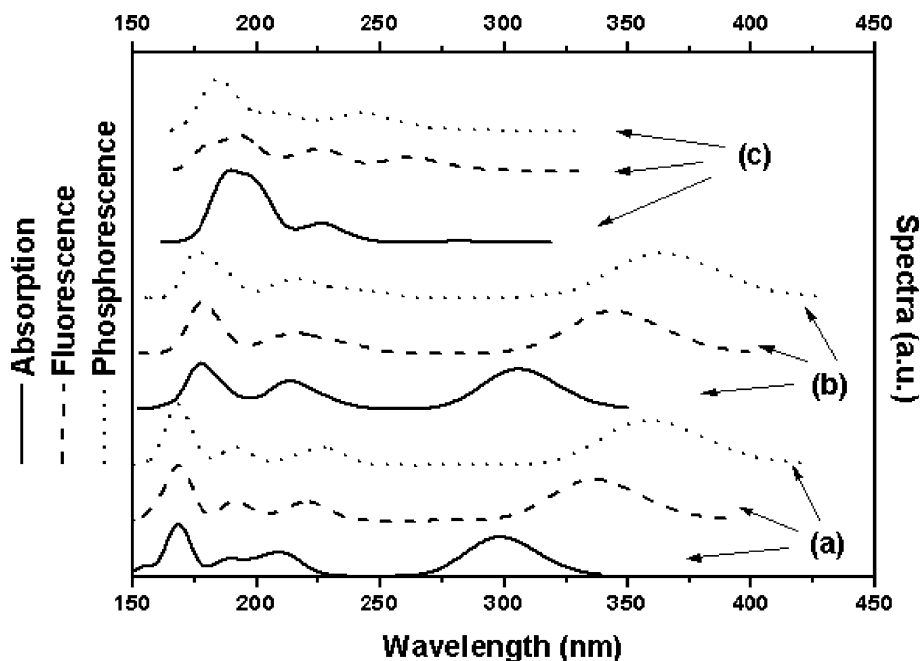


Fig. 5. Theoretical INDO/S-CI (absorption) and DNdM-INDO/S-CI (emission) UV-VIS spectra for (a) TS, (b) TR and (c). DSS molecules by and using PM3/CI optimized geometries.

Table 1
Principal electronic UV-VIS absorption transitions as determined from INDO/S-CI calculations based on optimized PM3/CI ground-state geometries

Molecule	nm	Oscillator strengths	Absorption
TS	300	1.23	0.99 H → L⟩
	209	0.64	-0.71 H - 1 → L⟩ -0.64 H → L + 1⟩
	168	1.16	-0.73 H - 3 → L + 2⟩ 0.53 H - 2 → L + 3⟩
TR	304	1.14	0.94 H → L⟩
	213	0.54	0.65 H - 3 → L⟩ -0.50 H → L + 1⟩
	178	0.71	-0.43 H - 4 → L⟩ -0.48 H - 3 → L + 1⟩ -0.69 H - 2 → L + 3⟩
DSS	282	0.04	0.64 H → L⟩ -0.47 H - 1 → L⟩ 0.46 H - 4 → L + 3⟩
	226	0.37	-0.59 H - 1 → L + 2⟩ -0.36 H - 1 → L + 3⟩
	190	1.10	-0.53 H - 3 → L + 1⟩ -0.33 H → L + 5⟩

must remember that noticeable charge rearrangements were found for the TR and DSS but not for the TS molecule.

An analysis of the principal transitions present in the calculated fluorescence and phosphorescence spectra reveals that the $|L \rightarrow H\rangle$ transition is dominant for TS and TR but not in the case of the DSS molecule.

The unusually large value predicted for the singlet excited state dipole and the peculiar behavior of the absorption spectrum to DSS can be rationalized in terms of the differences in conformation for these molecules. While in all calculations we have found the optimized conformation of the TS and TR molecules to be planar, the optimized DSS geometry corresponds to a sharply twisted conformation of the rings.

4. Summary

In this work we have used the PM3/CI, INDO/S-CI and DNdM-INDO/S-CI methodologies to

investigate the first excited states of resveratrol and structurally related stilbenes. The knowledge acquired from the comparison of the electronic charge distributions and corresponding absorption and emission spectra of these molecules can give us more insight on the biological action of resveratrol. From the above results we have identified promising active sites in the TR molecule that could be involved in its eventual pharmacological activity. In principle, it could be possible to improve the antioxidative activity of *trans*-resveratrol and structurally related molecules by suitable chemical modifications that should combine an increase of the charge density at these specific sites to a controlled internal charge transfer upon photoexcitation. As further theoretical and experimental investigations are needed to test this hypothesis, at present, additional work in this direction is in progress.

Acknowledgements

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