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Density functional study of the antioxidant activity of some recently synthesized resveratrol analogues

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ABSTRACT

In this paper we have investigated the two main working mechanisms (H atom and single-electron transfer) of five new potential antioxidant analogues of *cis*-resveratrol. The O–H bond dissociation energy (BDE) and ionization potential (IP) key parameters were computed in methanol. Results obtained indicate that all the examined compounds are more efficient antioxidants than the molecule from which they derive, mainly due to their higher degree of conjugation and the capability to delocalize the π-electrons which contribute to the stabilization of the radical species. The enhancement of these stabilizing effects is in part a result of the introduction of a single bond between the C2′ and C6 carbon atoms of *cis*-resveratrol that generates a new central aromatic ring. However, the number of hydroxyl groups and in particular the presence of the catechol moiety remains the most significant features in determining the order of radical scavenging potentiality. Spectroscopic UV–Vis characterization is also reported and discussed.

1. Introduction

Due to their incomplete electron shell, free radicals are unstable systems that react more with nearby molecules causing damage to the human body cells. Recent findings have shown that the damages induced by the free radicals lead to certain types of cancer. Antioxidants are substances able to prevent or reduce the risk of cancer binding free radicals and stabilizing them.

A well equilibrated diet which comprises, amongst other nutrients, good amounts of fruits, vegetables, whole grains, nuts, or their processed derivatives normally provides the consumer with sufficient antioxidants, avoiding the need for further supplementation. Among the naturally-occurring antioxidants, resveratrol (3,5,4′-trihydroxy-stilbene), an abundant constituent of grape, red wine and other food products (Burns, Yokota, Ashihara, Lean, & Crozier, 2002), has been widely investigated for its positive effects in cancer prevention, cardiovascular protection, and anti-aging (Smoliga, Baur, & Hausenblas, 2011). The studies devoted to antioxidant activity of resveratrol (Amorati et al., 2004; Cao et al., 2003; Iuga, Alvarez-Idaboy, & Russo, 2012; Leopoldini, Russo, & Toscano, 2011; Wang, Jin, & Ho, 1999), have established the 4′-OH in the stilbene scaffold to be responsible for the antioxidant activity (Cao et al., 2003; Caruso, Tanski, Villegas-Estrada, & Rossi, 2004; Queiroz, Gomes, Moraes, & Borges, 2009; Stojanovic & Brede, 2002; Wang et al., 1999).

Between the two isomeric forms of resveratrol (*cis* and *trans*), the *cis*-one was proved to be less efficient as an antioxidant (Mikulski, Górniak, & Molski, 2010) and can be easily isomerised into *trans*-resveratrol. The structural simplicity of this molecule, characterized by a double bond connecting the two phenolic rings, has stimulated interest in designing novel analogues with improved antioxidant capacity.

Recently, five *cis*-resveratrol analogues (Fig. 1) differing in the number and position of the hydroxyl groups were designed and synthesized (Ding et al., 2012). The introduction of a single bond linkage between C2′ and C6 in the structure of *cis*-resveratrol, other than preventing the rotation of the olefinic bridge, generates a phenanthrene ring which provides an extended conjugation of these systems. Such systems, therefore, would have higher capacity to stabilize, through resonance delocalization, the phenoxyl radicals formed in antioxidant reactions of the hydroxylated phenanthrenes.

The most well-known mechanisms by which antioxidants exert their action against free radicals involve the so called hydrogen atom transfer (HAT) or single electron transfer (SET) (Galano, 2011; Leopoldini, Marino, Russo, & Toscano, 2004a; Pérez-González & Galano, 2012; Wright, Johnson, & DiLabio, 2001) and a metal chelation process that prevents the Fenton reaction (Jovanovic, Steenken, Simic, & Hara, 1998; van Acker, de Groot, et al., 1996; van Acker, van den Berg, et al., 1996). In both the HAT and SET mechanisms, the evaluation of the antioxidant activity is usually done by determining the bond dissociation enthalpy (BDE) and the ionization potential (IP), respectively. In fact, low values of BDE or IP indicate an easier dissociation or electron abstraction, a better interaction with the free radicals and consequently a higher antioxidant activity of the compound.

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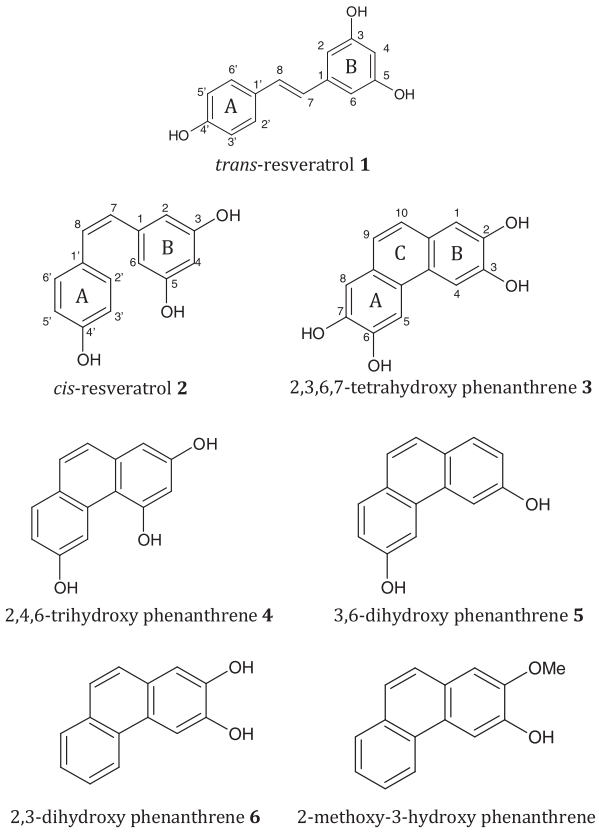

Fig. 1. Schematic drawing of all the examined compounds.

Studying the antioxidant activity of the five *cis*-resveratrol analogues (Fig. 1) by ferric reducing antioxidant power (FRAP), 2,2-diphenyl-1-picrylhydrazyl free radical scavenging (DPPH), and DNA strand breakage-inhibiting assays, corresponding to their electron-donating, hydrogen transfer and DNA-protecting abilities, respectively, Ding et al. (2012) found that the number and the position of the hydroxyl groups affect significantly the above properties. Many of these analogous were found to be more effective than *cis*-resveratrol and in particular, considering all the results from the various experiments, the compound 2,4,6-trihydroxyl phenanthrene, that presents the same hydroxyl group substitutions as resveratrol and the possibility to extend the electronic conjugation over multiple aromatic rings, seems to respond better to all needs including the ability to protect DNA.

In the present work, the results obtained in the experimental study of Ding et al. (2012), will be compared with those deriving by a theoretical density functional investigation aimed to explore HAT and SET mechanisms. Computations have been performed in methanol, which is the same medium used in the above mentioned experimental work. In particular, we have evaluated the conformational and electronic features of the five *cis*-resveratrol analogues and the effect of the functional groups on their antioxidant ability. The spin densities were reported to give better insight into delocalization of the unpaired electron and conjugation effects. Furthermore, in order to complete the spectroscopic characterization, the UV–Vis absorption spectra of all the examined compounds were reproduced and interpreted.

2. Methods

All quantum-chemical calculations were performed using the Gaussian 03 computational package (Frisch et al., 2004). The geometries of all the phenolic compounds investigated were fully optimized in methanol medium at the DF level by employing the hybrid exchange functional by Becke (B3) in combination with the Lee, Yang, and Parr (LYP) correlation functional (Becke, 1993; Lee, Yang, & Parr, 1988). The optimization calculations were performed by using the basis set 6-31+G** for all the atoms. The solvation effects were computed by means of the Conductor Polarizable Continuum Model (CPCM) (Cossi, Rega, Scalmani, & Barone, 2003) as implemented in Gaussian 03. The UAHF set of radii has been used to build-up the cavity. Harmonic vibrational frequencies were performed for both the compounds and their radicals to characterize all their conformations as minima.

The unrestricted open-shell approach was used for radical species. No spin contamination was found for all the radicals, and the $\langle S^2 \rangle$ value about 0.750 in all cases.

Final energies have been calculated by performing single-point calculations on the optimized geometries at the same level of theory and employing the larger 6-311++G(3df,2p) standard basis set for all the atoms.

The total bond dissociation free solvation energy (BDE) and adiabatic ionization potential (IP) were calculated (at 298 K) as a difference of energy between the ArOH and ArO$^{\cdot}$ or ArOH$^{+\cdot}$ species according the following reactions, respectively:

$$\mathrm{ArOH} \rightarrow \mathrm{ArO}^{\cdot} + \mathrm{H}^{\cdot}$$

$$\mathrm{ArOH} \rightarrow \mathrm{ArOH}^{+\cdot} + \mathrm{e}^{-}$$

where ArOH indicates the antioxidant molecule. The products of these reactions with a free radical R$^{\cdot}$ are the inoffensive RH and R^{-} species and the ArO$^{\cdot}$ and the ArOH$^{+\cdot}$ radicals. However, even if the reactions lead to the formation of other radicals, they are both less reactive with respect to R$^{\cdot}$ because, as we will see, they are stabilized by several factors such as hydrogen bond formation, conjugation and resonance effects.

Absorption spectra were computed as vertical electronic excitations from the minima of the ground-state structures by using time-dependent density functional response theory (TD-DFT) (Casida, 1995) as implemented in the Gaussian 03 code (Stratmann, Scuseria, & Frisch, 1998). The TD-DFT calculations were carried out by using the standard 6-31+G** basis set and the same B3LYP exchange–correlation functional.

Computations of single-point spin densities were performed using the larger 6-311++G(3df,2p) standard basis set for the most stable radical and radical cations of all the phenolic compounds investigated.

3. Results and discussion

It is well known that the antioxidant activity of polyphenolic systems is closely related to their conformational, electronic and spectroscopic characteristics. The concomitant presence of many hydroxyl groups, especially if mutually arranged in an *ortho* or *para* position, and the planarity that distinguishes these systems, are crucial for a good activity. Polyphenols, usually, pursue their antioxidant activity reacting with free radicals by donating to them a H atom or an electron and generating new radical species, knowledge of structural and electronic characters of which is essential for elucidating their scavenger behaviour. Systems with multiple OH groups can give rise to several radicals depending on the group which is radicalized.

In Fig. 1, we report the schematic drawing of all the examined compounds together with that of *cis*-resveratrol that is the system from which they derive and that of *trans*-resveratrol taken as a reference in the computations of relative binding energies. The labels for *cis*- and *trans*-resveratrol are those commonly used for these