Research Article

Antioxidant of *Trans*-Resveratrol: A Comparison between OH and CH Groups Based on Thermodynamic Views

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Trans-resveratrol establishes the planarity in its structure which makes it an interesting compound in both experimental and theoretical examinations. The current study, using the density functional method (DFT), attempts to compare the antioxidative capacities between hydroxyl (OH) and aromatic methine (CH) groups of this molecule. Becke's exchange-correlation B3LYP functional together with 6-311++G(d, p) basis set was used to reveal the effects of structural geometry and electronic feature on the antioxidative results of OH and CH groups. The antioxidative action of *trans*-resveratrol has followed the HAT mechanism in gas, but the SPLET pathway in liquids. OH bond breaking is easier than CH bond disruption. 4-OH bond breaking induces the lowest BDE values of 74.4–77.9 kcal/mol in gas, acetone, methanol, and water, as well as the lowest PA values of 37.2–46.2 kcal/mol in acetone, methanol, and water. From the kinetic view, 4-OH is also an active center to capture laboratory radical DPPH, ROS radicals $\text{HOO}^\bullet$ and $\text{CH}_3\text{O}^\bullet$, and RNS radical $^\bullet\text{NO}_2$.

1. Introduction

Trans-3,5,4'-trihydroxystilbene, which locally named *trans*-resveratrol (RSV), is an active polyphenol found in various medicinal plants, especially in berries, grapes, peanuts, and red wines [1, 2]. RSV demonstrates more stability than its geometric *cis*-form in a solid state [3], and its biosynthesis is due to the activation of enzyme resveratrol synthase [4]. From the view of previous preclinical research, RSV itself is shown to possess a wide range of biological activities, which may be possibly employed for the prevention and treatment of cancers, cardiac diseases, neurodisorders, and so on [5]. Antioxidative capacity is the best feature to explain its biological effects. For instance, RSV decreased the death of neuronal cells in Alzheimer's disease because it controlled the peroxidation of human low-density lipoprotein (LDL) in PC-12 cells [6]. RSV also acted as a useful antioxidant capturing free radicals in embryonic mesencephalic cells [7]. Besides the inhibitions of reactive oxygen species (ROS) radicals, such as hydroperoxide ($\text{HOO}^\bullet$) and methoxy

($\text{CH}_3\text{O}^\bullet$), RSV and its oxygenated analogs were further recognized as a significant agent against reactive nitrogen species (RNS) radicals like nitric oxide ($^\bullet\text{NO}$) and nitric dioxide ($^\bullet\text{NO}_2$) [8].

Although there are a number of DFT-computational reports on the antioxidative capacity of this molecule and its analogs [9, 10], specifically theoretical research using the combination of thermodynamic views is quite limited. Hence, this study aimed to make a comparative highlight between hydroxyl (OH) and methine (CH) groups of RSV in the antioxidative treatment. The potential functional groups with the lowest bond disruption energies are going to further interact with the ROS ($\text{HOO}^\bullet$ and $\text{CH}_3\text{O}^\bullet$) and RNS ($^\bullet\text{NO}$ and $^\bullet\text{NO}_2$) radicals, to gain insight into their kinetic mechanisms. To the best of our knowledge, the applications of RNS radicals in the calculated studies on the antioxidants of stilbenoids are very rare. Based on the DFT method/B3LYP functional coupled with 6-311++G(d, p) basis set, we carried out a calculated thermodynamic experiment on molecule RSV in both gas and liquids (acetone, methanol,

and water) to examine the effects of structural and electronic factors on the antioxidative powerful of this compound.

2. Theoretical Methodology

All the calculated actions in this work have been performed using Gaussian 09 software package [11]. The B3LYP/6-311++G(d, p) level is utilized to gain the optimized structural RSV and its cations, anions, and radicals since the calculations were taken into account in four media, including gas with the dielectric constant $\epsilon=1.00$, water ($\epsilon=78.32$), methanol ($\epsilon=32.60$), and acetone ($\epsilon=20.72$) [12]. The vibrational frequencies, at the same level of theory, have been calculated for correcting zero-point energy (ZPE), confirming that there are no imaginary frequencies in the ground states. The effects of liquids have been considered by using IEF-PCM (integral equation formalism polarizable continuum model) [13, 14].

As mentioned in previous research, the scavenging procedures of ROS and RNS radicals of RSV were ruled following the three well-known ways [15–17].

2.1. HAT (*H Atom Transfer*) Mechanism. The HAT procedure involved the splitting of the hydrogen atom of RSV and then moving to radical $R^\bullet$. This action was recognized as a homolytic reaction with the characteristic BDE (bond dissociation enthalpy):

$$\begin{aligned} \text{BDE} &= \Delta H(\text{RSV} - \text{O}^\bullet) + \Delta H(\text{H}^\bullet) - \Delta H(\text{RSV} - \text{OH}) & \text{or} \\ \text{BDE} &= \Delta H(\text{RSV} - \text{C}^\bullet) + \Delta H(\text{H}^\bullet) - \Delta H(\text{RSV} - \text{CH}) \end{aligned}$$

2.2. SET-PT (*Single Electron Transfer-Proton Transfer*) Mechanism. As shown in equation (2), the SET-PT mechanism consisted of two steps. In the first step, the parent molecule RSV extracted an electron to form $\text{RSV} - \text{OH}^{\bullet+}$ (or $\text{RSV} - \text{CH}^{\bullet+}$). This action was driven by the IP (ionization potential). In the second stage, $\text{RSV} - \text{OH}^{\bullet+}$ (or $\text{RSV} - \text{CH}^{\bullet+}$) continued to deprotonate. The PDE (proton dissociation enthalpy) was a characteristic of this step.

$$\begin{aligned} \text{IP} &= \Delta H(\text{RSV} - \text{OH}^{\bullet+}) + \Delta H(e^-) - \Delta H(\text{RSV} - \text{OH}) & \text{or} \\ \text{IP} &= \Delta H(\text{RSV} - \text{CH}^{\bullet+}) + \Delta H(e^-) - \Delta H(\text{RSV} - \text{CH}) \\ \text{PDE} &= \Delta H(\text{RSV} - \text{O}^\bullet) + \Delta H(\text{H}^+) - \Delta H(\text{RSV} - \text{OH}^{\bullet+}) & \text{or} \\ \text{PDE} &= \Delta H(\text{RSV} - \text{C}^\bullet) + \Delta H(\text{H}^+) - \Delta H(\text{RSV} - \text{CH}^{\bullet+}) \end{aligned}$$

2.3. SPLET (*Sequential Proton Loss Electron Transfer*) Mechanism. From equation (3), the SPLET mechanism was divided into two consecutive actions: the production of $\text{RSV} - \text{O}^-$ (or carbanion $\text{RSV} - \text{C}^-$) anion was due to the deprotonated phenomenon of $\text{RSV} - \text{OH}$ (or $\text{RSV} - \text{CH}$) in the first step; the electron transfer from $\text{RSV} - \text{O}^-$ (or $\text{RSV} - \text{C}^-$)

anion was sequential in the second step. The PA (proton affinity) and the ETE (electron transfer enthalpy) can be seen as characteristics of the first and second steps, respectively.

$$\begin{aligned} \text{PA} &= \Delta H(\text{RSV} - \text{O}^-) + \Delta H(\text{H}^+) - \Delta H(\text{RSV} - \text{OH}) & \text{or} \\ \text{PA} &= \Delta H(\text{RSV} - \text{C}^-) + \Delta H(\text{H}^+) - \Delta H(\text{RSV} - \text{CH}) \\ \text{ETE} &= \Delta H(\text{RSV} - \text{O}^\bullet) + \Delta H(e^-) - \Delta H(\text{RSV} - \text{O}^-) & \text{or} \\ \text{ETE} &= \Delta H(\text{RSV} - \text{C}^\bullet) + \Delta H(e^-) - \Delta H(\text{RSV} - \text{C}^-) \end{aligned}$$

In the DFT method, at $T=298\text{ K}$, the total enthalpy $\Delta H(A)$ of the species A is shown as follows [12]:

$$\Delta H(A) = E_O + \text{ZPE} + \Delta H_{\text{trans}} + \Delta H_{\text{rot}} + \Delta H_{\text{vib}} + RT \quad (4)$$

where E_O and ZPE were assigned to the total electronic and zero-point energies, respectively. ΔH_{trans} , ΔH_{rot} and ΔH_{vib} represented the translational, rotational, and vibrational contributions to enthalpy.

The enthalpies of electron and proton were collected from previous references [14], in which $\Delta H(e^-) = 0.75\text{ kcal/mol}$, -25.08 kcal/mol , -20.54 kcal/mol , and -28.43 kcal/mol were applied to the enthalpies of the electron in gas, water, methanol, and acetone, respectively. Similarly, $\Delta H(\text{H}^+) = 1.48\text{ kcal/mol}$, -244.15 kcal/mol , -247.97 kcal/mol , and -255.61 kcal/mol were used for the enthalpies of proton in gas, water, methanol, and acetone, respectively.

Additionally, the antioxidant of a systematic molecule might be further evaluated by physicochemical parameters [15], containing ϵ_{HOMO} (the energy of the highest occupied molecular orbital), ϵ_{LUMO} (the energy of the lowest unoccupied molecular orbital), spin density, electron affinity (EA), ionization potential (IP_o), chemical hardness (η) and chemical potential (μ), electronegativity (χ), global electrophilicity index (ω), and Fukui indices.

As a result of the finite difference approximation, these physicochemicals may have close relationships as follows:

$$\text{IP}_o \approx -\epsilon_{\text{HOMO}}, \quad (5)$$

$$\text{EA} \approx -\epsilon_{\text{LUMO}}, \quad (6)$$

$$\eta \approx \frac{(\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}})}{2}, \quad (7)$$

$$\mu = -\chi \approx \frac{(\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})}{2}. \quad (8)$$

The global electrophilicity index ω indicated the stabilization in the energy of a molecule since it accepted electrons from the environment. As a result, the higher ω^+ is turned out to be the better electron acceptance (electrophilic feature), while the higher ω^- means the better electron donation (nucleophilic feature). These indices are also related to μ , η , EA, and IP_o by

$$\omega = \frac{\mu^2}{2\eta}, \quad (9)$$

$$\omega^- = \frac{(3IP_o + EA)^2}{[16(IP_o - EA)]}, \quad (10)$$

$$\omega^+ = \frac{(IP_o + 3EA)^2}{[16(IP_o - EA)]}. \quad (11)$$

Fukui numbers were, shortly, the reactivity indices that provided useful information about an atom of a molecule that had a larger trend to donate or accept an electron. Three chemical Fukui indices f_x^+ , f_x^- , and f_x^o characterized electrophilicity, nucleophilicity, and radical attack affinity of atom X in molecule Y (of Z electrons), respectively (equations (12)–(14)).

Electrophilicity of atom Z in molecule Y (of Z electron) is

$$f_x^+ = P_x(Z+1) - P_x(Z). \quad (12)$$

The nucleophilicity of atom Z in molecule Y (of Z electron) is

$$f_x^- = P_x(Z) - P_x(Z-1). \quad (13)$$

Radical attack affinity is

$$f_x^o = \frac{[P_x(Z+1) - P_x(Z-1)]}{2}, \quad (14)$$

where P stands for the electronic population of atom X in molecule Y.

The conventional transition state theory (TST) has considerably studied the kinetic reactions of RSV with representative ROS and RNS radicals [12–17], in which the rate constant K was relative to Planck constant h , Boltzmann constant k_B , temperature T , the Wigner coefficient κ , and the Gibbs energy of activation $\Delta G^\ddagger$ as follows:

$$k(T) = \kappa \frac{T \cdot k_B}{h} e^{-\Delta G^\ddagger/RT}, \quad (15)$$

where $\Delta G^\ddagger$ is obtained at 298.15 K describing the deviation energy between transition state and reactant.

3. Results and Discussion

3.1. Geometrical Analysis. Studying the detailed geometry is necessary since the antioxidative results have deeply depended on the role of OH and CH groups in compound RSV. The general structure of RSV and its radical cases are depicted in Figure 1. Due to the symmetric property, 11-OH is identical with 13-OH, and the same phenomenon is applied to three pairs of 2-CH and 6-CH, 3-CH and 5-CH, and 10-CH and 14-CH. The optimized structure of RSV is the same in the four studied media gas, acetone, methanol, and water at B3LYP/6-311++G(d,p) level of theory, in which phenyl ring A sets the coplanarity with phenyl ring B via *trans*-double bond (both dihedral angles θ_{11} (C2–C1–C7–C8) and θ_{12} (C7–C8–C9–C14) reach 180° in all studied media) (Table 1 and Figure S1). Lu et al. (2013)

suggested that a planarity molecule with more electron delocalization will support the formation of its radicals, thereby having better nonplanarity substances in anti-oxidative treatments [10]. The bond distance of OH groups ranges from 0.962 to 0.965 Å compared with that of CH groups (1.082–1.087 Å). It is opposite to the decrease (0.001–0.002 Å) of 8-CH and 12-CH bond lengths, and 4-OH, 11/13-OH, and 3/5-CH bond lengths have slightly increased from 0.001 to 0.003 Å when gas changed to liquids, but the bond distance of aromatic methines 3/6-CH, 7-CH, and 10/14-CH keeps unchanged.

Studying the dependence of the potential energies on dihedral angles further confirms the coplanarity between ring A and ring B. The B3LYP functional couples with 6-31+G(d) basis set are used for the scanning progress to find the optimized energies since two torsional angles θ_{11} and θ_{12} have been changed with a step of 5° increase from –180° to 180°. The results are displayed in Figure 2 and Table S1. The first scanning action is applied to θ_{11} , by which minimal conformer lies at $\pm 170^\circ$ and $\pm 10^\circ$ and the barrier peaks at $\pm 90^\circ$ with the highest interconversion energy $\Delta E = 4.79$ kcal/mol. Regarding the second scanning step of θ_{12} , the absolute minimum is located at $\pm 180^\circ$ and 0° and two barriers state at -100° and 90° ($\Delta E = 4.77$ kcal/mol).

3.2. Frontier Molecular Orbital (FMO) Analysis and Molecular Electrostatic Potential Model (MEP). The FMO is a visible reality model to consider the delocalization of electrons and to predict good sites for radical quenching actions because the H-removal reaction has undergone the electron transfer [18]. At the DFT-B3LYP/6-311++G(d,p) level, HOMO neutral depositions did not show any difference in the four studied media, and LUMO neutral images were to do so. The electrons are distributed in the whole HOMO and LUMO neutral forms (Figure 3). Although 4-OH and 11(13)-OH radicals have similarity in HOMO plots, the electrons are only found in ring A of LUMOs of 11(13)-OH radicals. It suggests that 4-OH is an active site and better than 11(13)-OH in any type of reaction.

Taking CH cases into account, the electrons delocalize over HOMOs of 2(6)-CH, 3(5)-CH, 10(14)-CH, and 12-CH radicals, while LUMO pictures are associated with high concentration at ring A in 2(6)-CH and 3(5)-CH radical cases and ring B in 10(14)-CH and 12-CH radical cases. Resembling the results of the neutral case, HOMO and LUMO illustrations of 7-CH radical have no difference, which is accompanied by the absence of the electrons in ring B. Similarly, HOMO and LUMO of 8-CH radical show the same way, and the absence of electrons happens in ring A. It is possible to conclude that the energy necessary for breaking CH of the double bond may be less than that for CH of ring A or ring B.

As shown in equations (5) and (6), ϵ_{HOMO} and the ϵ_{LUMO} are opposite to IP_o and EA , respectively. The higher ϵ_{HOMO} represents the better electrons-giving, the lower ϵ_{LUMO} implies the better electrons-receiving, and the lower $\epsilon_{\text{gap}} = \epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}$ shows that the electrons transfer happens easier. As shown in Table 2, the gaseous phase

FIGURE 1: Resveratrol and its proposal radical cases.

TABLE 1: Bond distances and dihedral angles [$\theta_{11}(\text{C2-C1-C7-C8})/\theta_{12}(\text{C7-C8-C9-C14})$] of the optimized RSV in gas, acetone methanol, and water media at B3LYP/6-311++G(d, p) level of theory.

Mediums	Bond lengths								Dihedral angles	
	4(O-H)	11/13(O-H)	2/6(C-H)	3/5(C-H)	7(C-H)	8(C-H)	10/14(C-H)	12(C-H)	θ_{11}	θ_{12}
Gas	0.963	0.962	1.085	1.083	1.087	1.087	1.082	1.087	180	180
Acetone	0.965	0.965	1.085	1.084	1.087	1.086	1.082	1.085	180	180
Methanol	0.965	0.965	1.085	1.084	1.087	1.086	1.082	1.085	180	180
Water	0.965	0.965	1.085	1.084	1.087	1.086	1.082	1.085	180	180

FIGURE 2: The potential energy curves versus the dihedral angles $\theta_{11}(\text{C2-C1-C7-C8})$ and $\theta_{12}(\text{C7-C8-C9-C14})$ in the gaseous medium at B3LYP/6-31 + G(d) level of theory.

FIGURE 3: HOMO and LUMO images of structural neutral and radicals and band gap energies $\epsilon_{\text{gap}} = \epsilon_{\text{HOMO}} - \epsilon_{\text{LUMO}}$.

TABLE 2: Chemical reactivity indices obtained using the DFT method in gas, acetone methanol, and water media at B3LYP/6-311++G(d, p) level of theory.

No	η (eV)	χ (eV)	μ (eV)	IP _o (eV)	EA (eV)	ω	ω^+ (eV)	ω^- (eV)	Polarizability (au)	ϵ_{HOMO} (eV)	ϵ_{LUMO} (eV)
Gas	1.979	3.639	-3.639	5.618	1.661	3.347	1.775	5.414	211.276629	-5.618	-1.661
Acetone	1.972	3.759	-3.759	5.731	1.786	3.581	1.948	5.707	283.699045	-5.731	-1.786
Methanol	1.975	3.762	-3.762	5.737	1.788	3.584	1.950	5.712	286.390126	-5.737	-1.788
Water	1.975	3.769	-3.769	5.744	1.794	3.596	1.959	5.728	289.156687	-5.744	-1.794

establishes the highest ϵ_{HOMO} , but solvents would help to reduce ϵ_{LUMO} . Band gap energy ϵ_{gap} runs in clear order: gas (3.957 eV) > water (3.950 eV) > methanol (3.949 eV) > acetone (3.945 eV). Hence, liquids are expected to facilitate the anti-oxidative reaction of RSV.

The distribution of the charges in a systematic molecule might be visible by the 3D-molecular electrostatic potential model (MEP). MEP would possibly help to determine electrical zones (positive, negative, without charge) [19]. The electric density has been increased, following a consistent order of the colors: red < orange < yellow < green < blue, where red and orange areas demonstrate the deepest negative charge (the best site for electrophilic attack), the blue area represents the deepest positive charge (the best site for nucleophilic attack), but green is a characteristic of zero charges [20]. MEP of RSV is presented in Figure S2, in which aromatic and olefinic carbons, especially oxygen atoms of OH groups, are mostly shown with yellow color. Three protons of OH groups are accompanied by a blue hue. It reflects the fact that OH groups of RSV have been regarded as nucleophiles [13].

3.3. Spin Density Distribution. Spin density is thought to be the electronic charge of radical after H-abstraction. The more the spin density extends, the easier the radical is formed. It also found that spin density shows the same trend with the gaseous BDE value because the smaller the spin density happens, the smaller the BDE energy is found [21]. The significant results in the calculated spin density of RSV are demonstrated in Figure 4. In general, spin density is found to evenly distribute in 4-OH, 11(13)-OH, 7-CH, and 8-CH radicals, but not in the other radical cases. For instance, carbons C-1, C-3, C-5, and C-8 bear positive charge while carbons C-2 and C-6 indicate a negative value in 4-OH radical. By this means, ring A facilitates to form 4-OH radical.

In the gaseous phase, spin densities of oxygen atoms make a clear arrangement: 4-O $\cdot$ (0.296) < 11(13)-O $\cdot$ (0.400) < 7-C $\cdot$ (0.688) < 8-C $\cdot$ (0.691) < 2(6)-C $\cdot$ (0.854) < 10(14)-C $\cdot$ (0.904) < 3(5)-C $\cdot$ (0.929) < 12-C $\cdot$ (0.937). Expectedly, the BDE outcomes vary accordingly.

3.4. Natural Bond Orbital Analysis (NBO). Studying natural bond orbital (NBO) property is recognized to be one of the best ways to gain deep information about the delocalization of the electrons. NBO resulted in conjugative and hyperconjugative interactions. According to the second-order perturbation theory, the electrons moving from filled NBO donor (n) to empty NBO acceptor (m) will produce the stable energy $E^{(2)}$ [22]:

$$E^{(2)} = E_{\text{nm}} = -q^n \frac{(F_{\text{nm}})^2}{(E_m - E_n)}, \quad (16)$$

where q^n and F_{nm} are orbital donor occupancy and off-diagonal NBO Fock matrix element, respectively. E_n and E_m are two diagonal elements.

From this equation, the higher energy $E^{(2)}$ means that the conjugative/hyperconjugative interactions have occurred more often and the electrons transfer from donating orbitals to accepting orbitals frequently observed, consequently expanding the conjugative system. We now consider NBO analysis for the studied compound RSV in the gaseous phase at B3LYP/6-311++(d, p) level of theory since the previous reports have not been performed in depth yet. In this molecule, five types of interaction, including $\pi \rightarrow \sigma^*$ or π^* , $\sigma \rightarrow \sigma^*$, $n \rightarrow \sigma^*$ or π^* , have been observed (S2). The occurrence of various interactions, such as conjugative interactions $\pi(\text{C1-C2}) \rightarrow \pi^*(\text{C3-C4})$ ($E^{(2)} = 115.68$ kcal/mol)/ $\pi^*(\text{C5-C6})$ ($E^{(2)} = 104.75$ kcal/mol) or hyperconjugative ones $\sigma(\text{C5-C6}) \rightarrow \sigma^*(\text{C4-C5})$ ($E^{(2)} = 400.05$ kcal/mol)/ $\sigma^*(\text{C4-O4})$ (the highest $E^{(2)} = 7973.08$ kcal/mol)/ $\sigma^*(\text{O4-H4})$ ($E^{(2)} = 862.13$ kcal/mol), is mainly caused by the stabilization of ring A. Hyperconjugative interaction type $\sigma \rightarrow \sigma^*$ is prevalent in ring B, and transitions $\pi(\text{C12-C13}) \rightarrow \pi^*(\text{C10-C11})$ ($E^{(2)} = 245.21$ kcal/mol)/ $\pi^*(\text{C9-C14})$ ($E^{(2)} = 182.95$ kcal/mol) have been key roles to stabilize ring B. Besides hyperconjugative transitions, conjugative interactions, e.g., $\pi(\text{C1-C2}) \rightarrow \pi^*(\text{C7-C8})$ ($E^{(2)} = 77.01$ kcal/mol), $\pi(\text{C9-C14}) \rightarrow \pi^*(\text{C7-C8})$ ($E^{(2)} = 103.35$ kcal/mol), and $\pi(\text{C7-C8}) \rightarrow \pi^*(\text{C1-C2})/\pi^*(\text{C5-C6})$, are also set up to stabilize the olefinic double bond bridge. Lone pairs of electrons from oxygen atoms also distributed significant interactions. As a representative instance, the far intramolecular hyperconjugative interaction $\text{LP(1)O11} \rightarrow \sigma^*(\text{O4-H4})$ gets the remarkable $E^{(2)}$ of 213.24 kcal/mol. Collectively, the charge distribution in compound RSV is deduced from intramolecular interactions. The electrons from OH and CH groups have greatly affected antiradical outcomes.

3.5. Electronic Properties. The global hardness η from equation (7) has been shown to represent the prohibition of charge transfer [23]. The studied compound RSV has the maximal and minimal η values of 1.979 eV and 1.972 in gas and acetone, respectively. RSV in the polar solvent methanol and water consists of the same η value of 1.975 eV (Table 2). The polarizability of RSV was also taken into account. By using the HSAB discipline, compound RSV has high oxidation/low polarizability in gas and acetone but low oxidation/high polarizability in the polar environmental methanol and water.

The conceptual electronegativity χ was introduced to determine a trend of an atom to have an affinity of a pair of electrons into itself, along with the fact that this parameter is in contrast to chemical potential μ . By Sanderson's theoretical rule, a substance with the high χ amount promptly establishes the state of equalization and a low reactivity [24]. The lower the χ value is, the easier the antioxidative reaction happens. The studied compound RSV shows the lowest χ value of 3.639 eV in gas but increases in the solvents (Table 2). Thus, gas is a convenient condition to reduce this parameter. The electrophilicity indices ω , ω^+ , and ω^- are much more dependent on the medium using. As can be seen in Table 2, both of them have increased following the change

FIGURE 4: Spin density distribution of structural radicals in the gaseous medium at B3LYP/6-311++G(d, p) level of theory.

from gas to liquids, and an order was established as gas (nonpolar) < acetone (weak polar) < methanol < water (strong polar). It is also noticeable that the ω^+ number is averagely 3-fold lower than the ω^- number in each studied medium. Resembling flavonoid, benzofuran, and alkaloid derivatives, stilbenoids of type RSV have a tendency to give electrons rather than receive electrons [13–15].

Parallel with the results in electronic features and FMO and NBO analyses, the condensed Fukui functions being one of the best reactivity indicators are applied to determine nucleophilic, electrophilic, or radical properties of each atom in the molecule. It turns out that $\Delta f_x = f_x^+ - f_x^- < 0$ describes the nucleophilicity, and $\Delta f_x > 0$ reveals the electrophilicity [25]. The gaseous Fukui numbers of each atom of RSV are shown in Table S2. It can be concluded that carbons C1, C2/C6, C9, and C10/C14 have been classified as electrophilic sites, whereas the considerable remaining atoms are classified as nucleophilic sites. The negative value of f_x^o characterizes the radical production. Except for carbons C11/C13 ($f_x^o = 0.04$), all remaining atoms contained the negative f_x^o

values. It can be argued that OH and CH groups of RSV are favorable sites for the free radical attack.

3.6. Antioxidant Mechanisms

3.6.1. HAT Mechanism. HAT procedure has been considered when the protons of hydroxy or methine groups of RSV were separated. The BDE number is the main indicator to evaluate this action. The BDE results are highly compatible with the above spin density findings. The bond disruption occurred at 4-OH inducing the lowest BDE values in all four studied media, especially the water BDE value of 74.4 kcal/mol. The energies for 11(13)-OH bond breaking are also significant since the BDE values are averagely 82.0 kcal/mol (Table 3). The BDE amounts of 4-OH and 11(13)-OH groups are found in the following order: Gas > acetone > methanol > water. It is assumed that when antiradical reactions take place, olefinic methines are always good sites rather than aromatic methines. Both 7-CH and 8-CH have been shown to associate with the BDE value of around 100.0 kcal/mol, as compared with those of aromatic

TABLE 3: The enthalpies at 298K for radicals of RSV at B3LYP/6-311++G(d, p) level of theory (in kcal/mol).

No	BDE				IP				PDE				PA				ETE			
	Gas	Acetone	Methanol	Water	Gas	Acetone	Methanol	Water	Gas	Acetone	Methanol	Water	Gas	Acetone	Methanol	Water	Gas	Acetone	Methanol	Water
4-OH	77.9	76.3	75.7	74.4					232.1	7.7	15.9	19.6	334.2	37.2	43.3	46.2	59.6	70.9	75.4	79.7
11(13)-OH	82.6	82.4	81.8	81.2					236.8	13.7	22.0	26.3	340.6	39.1	45.7	48.5	57.9	75.1	79.8	83.4
2(6)-CH	110.4	110.6	110.6	110.0					264.7	41.9	50.7	55.2	389.8	87.4	92.7	95.9	36.5	54.9	61.3	65.2
3(5)-CH	112.6	112.3	112.3	111.7	161.7	100.4	107.1	102.0	266.9	43.6	52.5	56.8	389.1	83.8	90.3	92.9	39.5	60.2	66.0	69.3
7-CH	100.0	100.4	99.9	99.3					254.3	31.8	40.0	44.4	383.5	84.7	90.7	93.4	32.5	47.5	53.0	56.5
8-CH	100.6	101.1	100.5	99.9					254.9	32.4	40.7	45.1	380.3	82.9	88.9	91.7	36.2	50.0	55.4	58.9
10(14)-CH	113.2	112.3	112.3	111.8					267.5	43.7	52.5	56.9	389.1	85.7	91.6	94.1	40.1	58.4	64.8	68.1
12-CH	112.7	113.8	113.3	112.7					266.9	45.2	53.5	57.9	369.5	73.0	79.2	82.1	59.1	72.6	77.8	81.4

methines (the BDE numbers of above 110.0 kcal/mol). Collectively, the antioxidant of RSV might be due to hydroxy bond breaking.

3.6.2. SET-PT and SPLET Mechanisms. The SET-PT and SPLET are two renowned pathways for describing the radical capture by natural products [26–28]. As demonstrated in equation (2), the SET-PT procedure has included two steps, but the first stage is more important than the second stage. This conclusion is also applied to the SPLET model [29]. Consequently, the calculations of the IP and PA parameters would help to determine the SET-PT and SPLET models, respectively.

In Table 3, the IP enthalpies of RSV are being run by the following order: Gas (167.1 kcal/mol) >> methanol (1067.1 kcal/mol) > water (102.0 kcal/mol) > acetone (100.54 kcal/mol). Hence, the weak polar solvent, like acetone, or the polar solvent, like water, will support electron extraction from the parent molecular RSV. The PDE amount is responsible for deprotonation from radical cation RSV-OH⁺ or radical carbocation RSV-CH⁺ in the second stage of the SET-PT model. Both OH and CH groups afforded the PDE values in liquids far less than in gas, and a clear order can be found: gas >> water > methanol > acetone. The PDE values also show the same tendency as the BDE values because of the following observation: OH < CH (olefinic) < CH (aromatic) in all studied media.

Taking notes on the first stage of the third SPLET pathway, the PA values are very sensitive to environmental changes, by which they drastically decreased when converting gas into liquids. In the same manner as the PDE results, the PA outcomes in each case are found to run as gas >> water > methanol > acetone. In solvents, the PA enthalpies of OH groups ranged from 37.2 kcal/mol to 48.5 kcal/mol, and the lowest values are assigned to 4-OH (37.2 kcal/mol) and 11(13)-OH (39.1 kcal/mol) in acetone. The PA enthalpy necessary for disrupting olefinic or aromatic CH bonds is estimated about 2 times higher than that of OH bonds. The trend of the ETE outcome in the second stage is opposite to the PA results, in which the ETE energies increased in liquids but tremendously decreased in gas. In each case, the ETE values have always orderly followed the following rule: gas < acetone < water < methanol. The lowest and highest ETE values of 32.5 kcal/mol and 83.4 kcal/mol belong to the 7-CH case in gas and 11(13)-OH case in methanol. Therefore, in contrast to the BDE findings, the gaseous electron transfers are facilitated at olefinic methine 7-CH.

3.6.3. Preferential Mechanisms. The propitious antioxidant mechanism of the studied compound RSV could be discussed via three main enthalpies BDE, IP, and PA [12–17, 29]. Comparing them, the minimal calculated result is desired, and the representative mechanism takes place easier. Table 3 evidently provided the results inducing an arrangement PA < BDE < PA in three solvents. Thus, the

HAT and SET-PT pathways did not possess a model as preferential as the SPLET model. However, considering these three indicators in the gaseous phase, the BDE numbers are lower than the IP and PA numbers. Hence, the HAT model should be suitable for gas. An additional remark is that RSV radicals formed by OH bond disruptions need to have lower energies than CH bond separation.

3.6.4. Kinetics of DPPH, ROS, and RNS Radical Attack on RSV. Although the studies on electronic and/or structural properties of RSV and its analogs are now available, kinetic views are quietly limited. We continued to set up a DFT calculated research on kinetic reactions when DPPH, ROS (HOO[•] and CH₃O[•]), and RNS ([•]NO and [•]NO₂) radicals attack RSV at the B3LYP/6-311++G(d, p) level of theory.

While DPPH radicals have been used frequently for antioxidative examination in laboratories [29–33], there have not been extensively DFT calculated approaches to report interactions between RSV and DPPH radicals, to date. In this paper, the kinetics between them in water is the first aim since RSV was typical compounds having good solubility in water [34]. The outcomes have been provided in Table 4 and Figures 5 and 6, and the attacks of DPPH radicals on OH and CH groups of RSV have undergone a transition state (TS). The lower $\Delta G^\ddagger$ and the higher K will cause better antiradical reactions [13, 14]. It makes a good agreement with the above findings of BDE and PA enthalpies; the lowest $\Delta G^\ddagger$ value of 21.4 kcal/mol and the highest K value of 1.338×10^3 L/mol s were assignable to 4-OH case, as compared with those of 11(13)-OH case ($\Delta G^\ddagger = 25.0$ kcal/mol, $K = 2.753 \times 10^1$ L/mol s). CH groups seem not to be active sites; they are composed of the high $\Delta G^\ddagger$ values of 54.8–58.1 kcal/mol and low K value of 5.903×10^{-14} – 1.158×10^{-13} kcal/mol. However, it should be noted that olefinic methines 7-CH and 8-CH have always the better $\Delta G^\ddagger$ and K values than those of aromatic methines. The different results between OH and CH groups are also observed in the optimized structural TSs. To interact with central radical nitrogen of DPPH, O...H bond lengths fluctuate from 1.164 to 1.176 Å, whereas C...H bond lengths are 1.515–1.537 Å in olefinic CH cases and 1.627–1.677 Å in aromatic CH cases (Figure 6). It can be predicted that the structural TSs of RSV-OH + DPPH are more stable than RSV-CH + DPPH.

From these prospects, we have further assessed when the natural ROS (HOO[•] and CH₃O[•]) and RNS ([•]NO and [•]NO₂) radicals attack two potential antioxidative sites 4-OH and 11(13)-OH in both water and gas at the same theoretical level. The results are summarized in Table 5 and Figures 7–9. 4-OH + CH₃O[•] has induced the lowest $\Delta G^\ddagger$ value of 6.0 kcal/mol and the highest K value of 1.237×10^{10} L/mol s in water, but the same result belongs to 11(13)-OH + CH₃O[•] in gas ($\Delta G^\ddagger = 2.5$ kcal/mol, $K = 5.709 \times 10^{11}$ L/mol s). 4-OH + CH₃O[•] in water also consists of the significant $\Delta G^\ddagger$ value of 7.1 kcal/mol and K value of 4.208×10^{09} L/mol s. With the better $\Delta G^\ddagger$ and K values, 4-OH + HOO[•] in water is

TABLE 4: DPPH radical attack on hydroxy and methine groups of RSV in water (calculated $\Delta G^\ddagger$ and K at the B3LYP/6-311++G(d, p) level of theory).

No	$\Delta G^\ddagger$ (kcal/mol)	K (L/mol.s)
DPPH + RSV		
4-OH	21.4	1.338×10^3
11(13)-OH	25.0	2.753×10^1
2(6)-CH	56.8	5.903×10^{-14}
3(5)-CH	55.5	2.195×10^{-13}
7-CH	54.8	4.954×10^{-13}
8-CH	55.1	3.645×10^{-13}
10(14)-CH	56.1	1.158×10^{-13}
12-CH	58.1	1.373×10^{-14}

FIGURE 5: Energy diagram for DPPH radical attack on hydroxyl and methine groups of RSV in the water at B3LYP/6-311++G(d, p) level of theory.

regarded as likely to happen easier than $4\text{-OH} + \bullet\text{NO}_2$. However, $11(13)\text{-OH} + \bullet\text{NO}_2$ in water is expected to be better than $11(13)\text{-OH} + \text{HOO}\bullet$. OH groups of RSV fail to control $\bullet\text{NO}$ radicals in water since the $\Delta G^\ddagger$ values were very high and the K values were very low (Table 5).

The gaseous $\Delta G^\ddagger$ findings run as follows: $11(13)\text{-OH} + \text{CH}_3\text{O}\bullet < 4\text{-OH} + \text{CH}_3\text{O}\bullet < 4\text{-OH} + \text{HOO}\bullet < 11(13)\text{-OH} + \text{HOO}\bullet < 4\text{-OH} + \bullet\text{NO}_2 < 11(13)\text{-OH} + \bullet\text{NO}_2 < 4\text{-OH} + \bullet\text{NO} < 11(13)\text{-OH} + \bullet\text{NO}$, while the gaseous K results

indicate the opposite trend. It can therefore be concluded that RSV-OH captured ROS radicals better than RNS radicals in gas. Another remarkable feature is that the gaseous bond lengths RSV-O...H in all reactions are always longer than those in water (Figure 9). Additionally, RSV-OH + $\bullet\text{NO}$ radicals in both two media yield to the bond lengths RSV-O...H (1.437–1.744 Å) longer than those of the remaining cases. Hence, the structural TSs formed by interacting with $\bullet\text{NO}$ radicals are unstable.

FIGURE 6: The optimized structures of transition states (TSs) when DPPH radicals attacked hydroxy and methine groups of RSV at B3LYP/6-311++G(d, p) level of theory.

TABLE 5: ROS and RNS attack on hydroxy groups of RSV in gas and water (calculated $\Delta G^\ddagger$ and K at the B3LYP/6-311++G(d, p) level of theory).

Radicals	No	$\Delta G^\#$ (kcal/mol)	K (L/mol s)	$\Delta G^\#$ (kcal/mol)	K (L/mol s)
		Water		Gas	
HOO•	4-OH	9.6	3.092×10^8	6.7	6.876×10^9
	11(13)-OH	13.6	4.523×10^6	9.5	3.640×10^8
CH ₃ O•	4-OH	6.0	1.237×10^{10}	2.6	4.350×10^{11}
	11(13)-OH	7.1	4.208×10^9	2.5	5.709×10^{11}
•NO	4-OH	34.2	1.246×10^{-3}	32.7	5.464×10^{-3}
	11(13)-OH	39.2	5.595×10^{-6}	37.8	2.538×10^{-5}
•NO ₂	4-OH	10.2	1.495×10^8	13.6	1.353×10^0
	11(13)-OH	11.0	6.456×10^7	17.0	3.793×10^{-2}

FIGURE 7: Energy diagram for HOO• and CH₃O• radical attack on hydroxy groups of RSV at B3LYP/6-311++G(d, p) level of theory.

FIGURE 8: Energy diagram for •NO and •NO₂ radical attack on hydroxy groups of RSV at B3LYP/6-311++G(d, p) level of theory.

FIGURE 9: The optimized structures of TSs when [•]HOO, CH₃O[•], [•]NO, and [•]NO₂ radicals attack hydroxy groups of RSV at B3LYP/6-311++G(d, p) level of theory.

4. Conclusion

This paper provides insights into the antioxidative procedure of the well-known stilbenoid RSV. Various chemical indicators such as chemical hardness, electron affinity, and ionization potential, together with FMO and NBO analyses, are useful for determining the structural-electronic effects on the reactivity of RSV. Antioxidative actions of RSV are mainly based on OH bond breaking rather than CH bond breaking. The antioxidative HAT and SPLET mechanisms are prevalent in the gaseous phase and solvents acetone, methanol, and water, respectively. 4-OH bond disruption associates with the lowest BDE value of 74.4 kcal/mol in water and the lowest PA enthalpy of 37.2 kcal/mol in acetone. From kinetic results, 4-OH and 11(13)-OH groups when interacting with DPPH radicals are more advantageous than CH groups. 4-OH + $\text{CH}_3\text{O}^\bullet$ showed the lowest $\Delta G^\ddagger$ value of 6.0 kcal/mol and the highest K value of 1.237×10^{10} L/mol.s in water, but the best $\Delta G^\ddagger$ value of 2.5 kcal/mol and K value of 5.709×10^{11} L/mol.s in gas are assigned to 11(13)-OH + $\text{CH}_3\text{O}^\bullet$. Finally, 4-OH that captures ROS type $\text{HOO}^\bullet$ and RNS type $^\bullet\text{NO}$ and $^\bullet\text{NO}_2$ radicals is better than 13-OH in both water and gas.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they do not have any conflicts of interest.

Supplementary Materials

Figure S1: the state forms of RSV in studied media at the B3LYP/6-311++G(d,p) level of theory. Figure S2: molecular electrostatic potential mapped on the isodensity surface of RSV at the B3LYP/6-311++G(d,p) level of theory in the gaseous phase. Table S1: the potential energies versus torsional angles (θ) at the B3LYP/6-31+G(d) level of theory. Table S2: NBO analysis of the charge delocalization in the gaseous medium at the B3LYP/6-311++(d,p) level of theory. (Supplementary Materials)

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