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Quantum-chemical Calculations of the Antioxidant Properties of *trans-p*-coumaric Acid and *trans*-sinapinic Acid

Alicja Urbaniak[1]*, Marcin Molski[1], Małgorzata Szeląg[2]

[1]*Department of Theoretical Chemistry, Faculty of Chemistry, A. Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland*
[2]*Department of Human Molecular Genetics, Faculty of Biology, A. Mickiewicz University, Umultowska 89, 61-614 Poznań, Poland*
** e-mail: au50380@st.amu.edu.pl*

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Abstract: *Trans-p*-coumaric and *trans*-sinapinic acids are cinnamic acid`s derivatives which show strong antioxidant properties. In this work full optimization of both chemical structures and their radical, cation radical and anionic forms in vacuum and water medium has been performed, and antioxidant descriptors: Bond Dissociation Enthalpy, Adiabatic Ionization Potential, Proton Dissociation Enthalpy, Proton Affinity, Electron Transfer Enthalpy, Gas Phase Acidity, Free Gibbs Energy have been calculated. The Highest Occupied and Lowest Unoccupied Molecular Orbital energies have been employed to determine groups in compounds studied with the highest electron density. All calculations were performed using Gaussian 03W software package at the DFT level of theory (B3LYP hybrid functional) together with 6-311+G(2d,2p) basis set. Strong antioxidant properties of both investigated compounds were determined in this study. Based on the results it may be suggested that *trans-p*-coumaric and *trans*-sinapinic acids react according to the Hydrogen Atom Transfer mechanism in vacuum and according to Single-Electron Transfer followed by the Proton Transfer mechanism in water medium. Moreover, in both compounds studied the O-H bond is a preferred place of free radical attack.

Key words: *trans-p*-coumaric acid, *trans*-sinapinic acid, antioxidant properties, DFT, C-PCM model, BDE, AIP, PDE, PA, ETE, HOMO and LUMO energy

I. INTRODUCTION

Free radicals are very reactive chemical species with an unpaired electron. Because of their reactivity lipids, proteins and DNA can be damaged by the radicals action. In consequence, they are responsible for many diseases, such as cancer [1-4], cardiovascular disorders [5-8], atherosclerosis [9-12], asthma, arthritis, neurodegenerative disorders: Alzheimer`s [13-17], Parkinson`s diseases and dementia [18]. Antioxidants are compounds of natural and synthetic origin with the capacity to scavenge free radicals, hence they have been studied intensively.

The *trans-p*-coumaric acid (3-(4-hydroxyphenyl)prop-2-enoic acid, Fig. 2.) as well as *trans*-sinapinic acid (3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid Fig. 3) are cinnamic acid`s ((*E*)-3-phenylprop-2-enoic acid, Fig. 1) derivatives. Both substances occur in nature: the *trans-p*-coumaric acid is present in plants (for example, in bamboo leaves [19]), microorganisms, animals [20], and is synthesized in the human liver [21], whereas the *trans*-sinapinic acid is present in edible plants and fruits [22-25] (broccoli, leafy brassicas and citrus juices). Antioxidant properties of the *trans-p*-coumaric acid were studied experimentally and theoretically [21, 26]. Because of its radical scavenging activity the *trans-p*-coumaric acid can reduce serum cholesterol level and decrease lipid peroxidation [21]. Moreover, together with caffeic and ferulic acids it can promote the excretion of natural sterols which leads to decreased absorption of dietary cholesterol [27]. The *trans*-sinapinic acid is a strong antioxidant [28-30], which is endowed also with anxiolytic [31] and anti-inflammatory properties [32]. The ability of the sinapinic acid to inhibit peroxynitrite-mediated oxidation related with its antioxidant properties has been confirmed by *in*

vitro experiments [33-34]. In comparison to other phenolic antioxidants, the sinapinic acid has stronger antioxidant properties than the ferulic acid, syringic acid and p-coumaric acid but a little bit lower than the curcumin and chlorogenic acid and much lower than caffeic and gallic acids [35-37]. For instance, in the DPPH (2,2-diphenyl-1-picrylhydrazyl) analysis the antioxidant properties of compounds change as: gallic acid > caffeic acid ~ ascorbic acid ~ Trolox > sinapinic acid > isoeugenol [37]. ABTS (2,20-azinobis(3-ethylbenzothiazoline-6-suslfonic acid) assay has shown that the sinapinic acid is a weaker antioxidant than the gallic acid but stronger than the rest of tested compounds [37]. CBA (Crocin Bleaching Assay) test has shown that the sinapinic acid is the strongest antioxidant of all investigated compounds [37]. In ORAC assay (Oxygen Radical Absorbance Capacity) only caffeic and isoeugenol have stronger antioxidant abilities than the sinapinic acid [37].

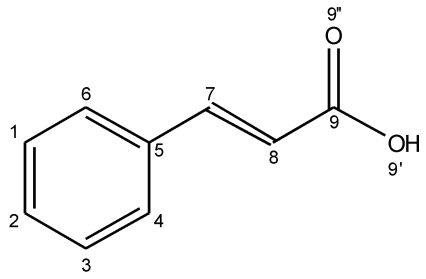

Fig. 1. Molecular structure of *trans*-cinnamic acid

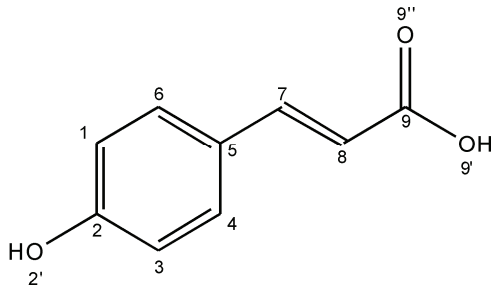

Fig. 2. Molecular structure of *trans*-*p*-coumaric acid

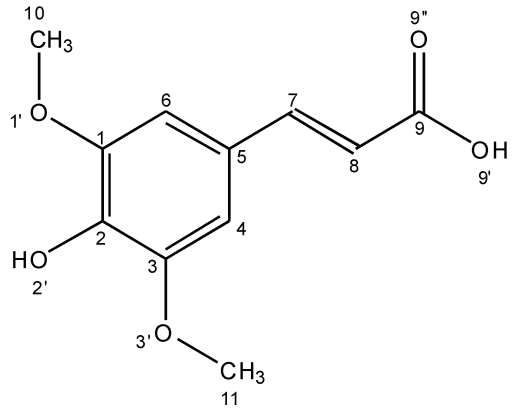

Fig. 3. Molecular structure of *trans*-sinapinic acid

There are five known antioxidant mechanisms which describe antioxidant reactions [38-47]:

1) HAT (*Hydrogen atom transfer*) mechanism:

$$ArOH + X^{\bullet} \rightarrow ArO^{\bullet} + XH \qquad (I.I)$$

According to this mechanism phenolic antioxidant reacts directly with a free radical which is neutralized, and a radical form of phenolic antioxidant appears. A numerical parameter associated with this mechanism is BDE (*Bond Dissociation Enthalpy*). The lower BDE parameter characterizes better antioxidant property.

2) SET (*Single electron transfer*) mechanism:

$$ArOH + X^{\bullet} \rightarrow ArOH^{\bullet+} + X^{-} \qquad (I.II)$$

A numerical parameter related with the SET mechanism is AIP (*Adiabatic Ionization Potential*).

3) SET-PT (*Single-electron transfer followed by proton transfer*):

1. $$ArOH + X^{\bullet} \rightarrow ArOH^{\bullet+} + X^{-} \qquad (I.III)$$

2. $$ArOH^{\bullet+} \rightarrow ArO^{\bullet} + H^{+} \qquad (I.IV)$$

This mechanism is a two-step reaction. In the first step a phenolic antioxidant molecule reacts with the free radical, and a cationic radical form of the phenolic antioxidant and an anionic form of the radical appear. This reaction is a thermodynamically significant step of this two-step mechanism. In the second step the cationic radical form of the phenolic antioxidant decomposes into a phenolic radical and proton. A numerical parameter related with the SET-PT mechanism is AIP (*Adiabatic Ionization Potential*) for the first step and PDE (*Proton Dissociation Enthalpy*) for the second step.

4) SPLET (*Sequential proton loss electron transfer*):

1. $$ArOH \rightarrow ArO^{-} + H^{+} \qquad (I.V)$$

2. $$ArO^{-} + X^{\bullet} + H^{+} \rightarrow ArO^{\bullet} + XH \qquad (I.VI)$$

This mechanism also consists of a two-step reaction. In the first step the phenolic antioxidant dissociates into an anionic form and proton, and then ions created in the first reaction react with the free radical. In this reaction a radical form of the phenolic antioxidant and a neutral molecule appear. A numerical parameter related with this mechanism is for the first reaction step: PA (*Proton affinity*) and for the second step: ETE (*Electron Transfer Enthalpy*). Coexistence of the presented mechanisms is shown in Fig. 4.

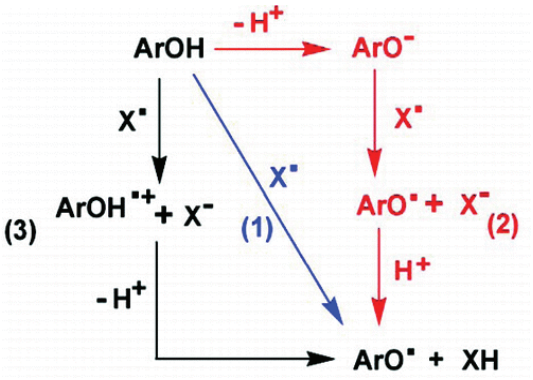

Fig. 4. Phenolic antioxidants-mechanisms of action: (1) HAT, (2) SPLET, (3) SET-PT. ArOH - phenolic antioxidant, $X^{\bullet}$ – free radical. From [48]

The other mechanism used to describe antioxidant properties is TMC (*Transition Metals Chelation*) [45]. Metals in their low oxidation state may generate free radicals according to the Fenton reaction:

$$H_2O_2 + M^{n+} \rightarrow HO^- + HO^{\bullet} + M^{(n+1)+} \qquad \text{(I.VII)}$$

$$ArOH \rightarrow ArO^- + H^+ \qquad \text{(I.VIII)}$$

In the TMC scheme each molecule which may dissociate has the ability to chelate heavy metals. Especially anions of polyphenols have the significant abilities to chelate heavy metals. Since chelation of metals often occurs due to deprotonated hydroxyls in the polyphenols, the ability of a molecule to produce the proton is taken into consideration. The numerical parameter related with this mechanism is *gas phase acidity* – it is identified with the vacuum enthalpy of the compound $\Delta H_{acidity}$. For the calculations in solvents the free Gibbs energy $\Delta G_{acidity}$ is calculated.

Other important descriptors of the antioxidant properties are distributions of HOMO and LUMO and spin density – SD of molecules. The lower HOMO energy is responsible for the poorer abilities of a molecule to donate a proton. Hence, the HOMO distribution reveals which chemical groups in a molecule are easily attacked by free radicals. The SD parameter characterizes the distribution of non-paired electron and the stability of a radical form of the molecule. From the difference between LUMO and HOMO energy we can conclude about chemical activity of the molecule. The lower ΔE(LUMO – HOMO) is connected with lower activity of the molecule [49].

The main aim of this work was to optimize structures of all the studied compounds: neutral, radical, cationic radical and anionic forms to explain the structure-antioxidant relationship. We had also been concerned with the calculation of antioxidant descriptors: BDE, AIP, PDE, PA, ETE, $\Delta H_{acidity}$, $\Delta G_{acidity}$ for *trans-p*-coumaric and *trans*-sinapinic acids. The next step was the determination of the preferred mechanism of antioxidation and calculation of HOMO and LUMO energies and transition energy between those states. All calculations were performed in vacuum and water medium.

II. COMPUTATIONS

All quantum-chemical calculations were performed using the Gaussian 03W [50] software package. Geometry of *trans-p*-coumaric and *trans*-sinapinic acids in their ground state were fully optimized in vacuum and water environment employing the DFT method with restricted B3LYP hybrid functional [51-53] together with 6-311 +G(2d,2p) basis set. However, for the optimization of the geometry of the radicals and cation radicals the unrestricted B3LYP/6-311+G(2d,2p) level of theory was applied. The optimization of the geometry of mono- and dianions was carried out with the rB3LYP/6-311+G(2d,2p). To decide which antioxidant mechanism is preferred for these two compounds the numerical descriptors: BDE, AIP, PDE, PA, ETE, $\Delta H_{acidity}$, $\Delta G_{acidity}$ defined below have been calculated.

$$BDE = H_{ArO}^{\bullet} + H_H^{\bullet} - H_{ArOH} \qquad \text{(II.I)}$$

in which $H_{ArO}^{\bullet}$ is the enthalpy of the radical, $H_H^{\bullet}$ is the enthalpy of the H atom, H_{ArOH} is the enthalpy of the compound.

$$AIP = H_{ArOH}^{\bullet+} - H_{ArOH} \qquad \text{(II.II)}$$

here $H_{ArOH}^{\bullet+}$ is the enthalpy of cationic radical, H_{ArOH} is the enthalpy of the compound.

$$PDE = H_{ArO}^{\bullet} + H_H^{+} - H_{ArOH}^{\bullet+} \qquad \text{(II.III)}$$

in which $H_{ArO}^{\bullet}$ is the enthalpy of the radical, H_H^{+} is the enthalpy of the proton, $H_{ArOH}^{\bullet+}$ is the enthalpy of cationic radical.

$$PA = H_{ArO}^{-} + H_H^{+} - H_{ArOH} \qquad \text{(II.IV)}$$

here H_{ArO}^{-} is the enthalpy of the anion, H_H^{+} is the enthalpy of the proton, H_{ArOH} is the enthalpy of the compound.

$$ETE = H_{ArO}^{\bullet} - H_{ArO}^{-} \qquad \text{(II.V)}$$

here $H_{ArO}^{\bullet}$ is the enthalpy of the radical, H_{ArO}^{-} is the enthalpy of the anion.

$$\Delta H_{acidity} = H_{ArO}^{-} - H_{ArOH} \qquad \text{(II.VI)}$$

in which H_{ArO}^{-} is the enthalpy of the anion, H_{ArOH} is the enthalpy of the compound.

$$\Delta G_{acidity} = G_{ArO^-} - G_{ArOH} \quad \text{(II.VII)}$$

here G_{ArO^-} is the Gibbs free energy of the anion, G_{ArOH} is the Gibbs free energy of the compound. To calculate the energy difference ΔE between LUMO and HOMO energies the following formula has been used:

$$\Delta E = E_{LUMO} - E_{HOMO} \quad \text{(II.VIII)}$$

All calculations carried out in water environment were performed with the C-PCM solvation model (*conductor–like polarizable continuum model*) [54]. The enthalpy values: $H(H^{\bullet})_{vacuum}$ = −0.49764 Ha (hartree) [55], $\Delta_{hydr}H(H^{\bullet})$ = −0.00152 Ha [56-57], $H(H^{+})_{vacuum}$= 0.00236 Ha [58], $\Delta_{hydr}H(H^{+})$ = −0.41516 Ha [59] were employed in calculations. Parameters describing the electron-donating abilities of *trans-p*-coumaric and *trans*-sinapinic acids (HOMO distribution and the SD distribution) were calculated in vacuum and in water environment at the B3LYP/6-311+G(2d,2p) level of the theory.

III. RESULTS

III. 1. Geometries

Geometry and the total molecular energy optimizations have been carried out in the vacuum without symmetry constraints in the ground state. Through the scanning of dihedral angles α = H_8-C_8-C_9-O_9, and θ = C_4-C_5-C_7-H_7, the

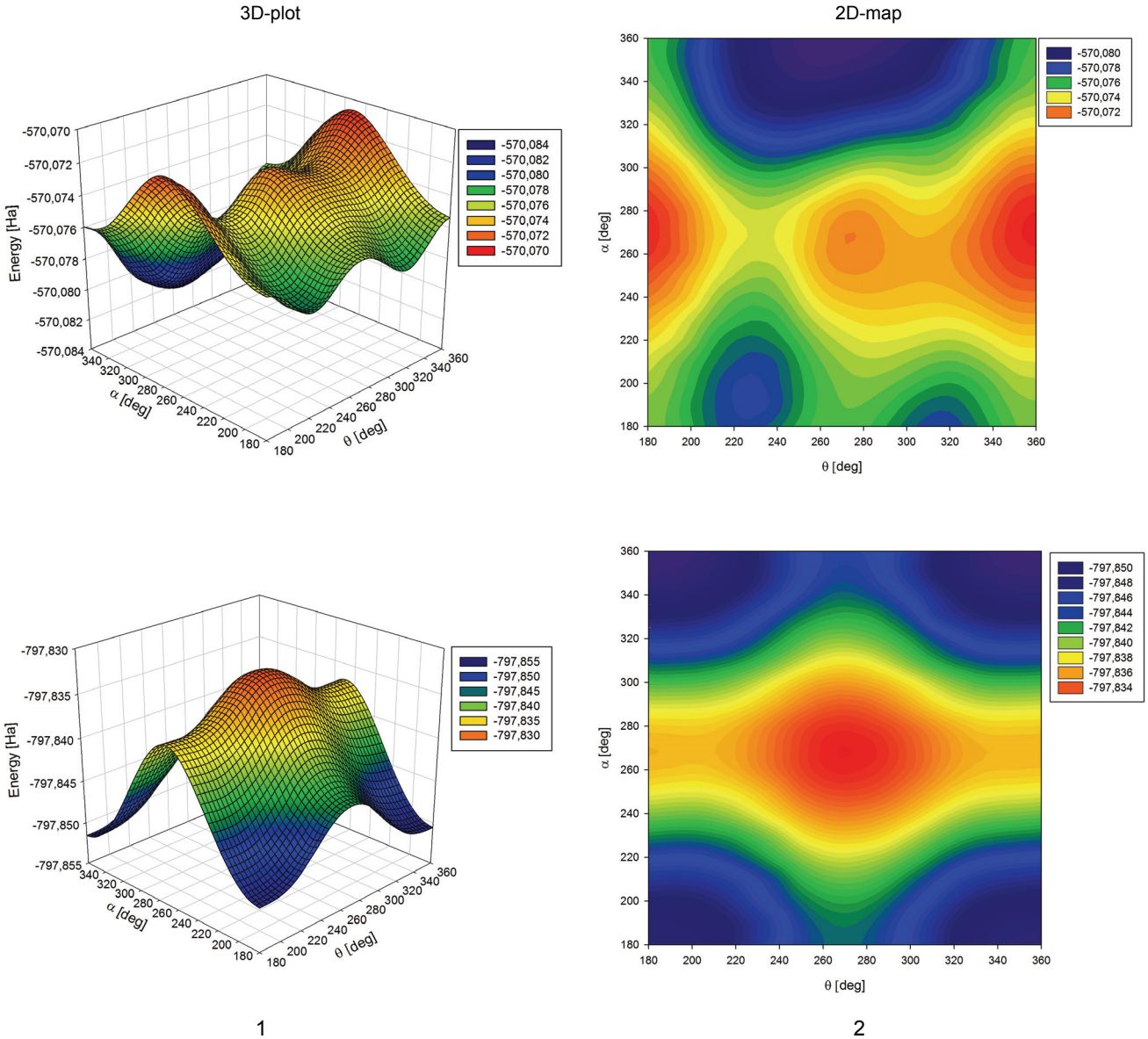

Fig. 5. 3D-plots and 2D-maps of PES for *trans-p*-coumaric acid (1) and *trans*-sinapinic acid (2) in vacuum

Potential Energy Surface profiles (3D-PES) were constructed. PES scans were calculated employing the HF method together with a 6-31G(d,p) basis set (Fig. 5) Dihedral angles were scanned in the range: $180^o \leq \alpha \leq 360^o$, $180^o \leq \theta \leq 360^o$. The angles α, θ describe the rotation around the C-C single bonds, as follows: C_8-C_9, C_5-C_7. From the most stable conformations with partial optimization on 3D-PES, the HF/6-31G(d,p) geometry optimization was performed to confirm the positions of the minima. Afterwards, the most stable structures obtained from the energy profiles were fully optimized. Geometry and energy optimization for all studied compounds (Fig. S.1. in Supplement) was made for isolated molecules in vacuum employing the DFT/rB3LYP method together with 6-311+G(2d,2p) basis set. Finally, for each fully optimized structure, the frequency analysis at rB3LYP/6-311+G(2d,2p) was performed to verify that the structures corresponded to stationary points on the PES. Thus the most reliable structures of *trans-p*-coumaric and *trans*-sinapinic acids in their absolute energy minimum have been determined. The same methodology was applied for calculations in water medium using the C-PCM solvation model. In all investigated structures the hydrogen atom from the hydroxyl group is planar with respect to the surface of the molecule. All studied geometries are planar in vacuum and in water medium. The planarity of the geometry influences the antioxidant activity because it causes delocalisation of the lone electron pair through the whole structure: the phenyl ring, vinyl bond and carboxyl group.

III. 2. Descriptors of antioxidant properties

BDE is a numerical parameter related with the HAT mechanism. It characterizes the stability of the bond 2`-O-H in the hydroxyl group. Calculated values of BDE are presented in Table 1. They reveal that the stability of the O-H bond in *trans-p*-coumaric acid is similar in vacuum and in polar medium. The stability of this bond is slightly lower in the *trans*-sinapinic acid than in the *trans-p*-coumaric acid.

Table 1. BDE values [kcal/mol] calculated on B3LYP/ 6-311+G(2d,2p) level of theory

Bond	BDE	
	Vacuum	Water
trans-p-coumaric acid 2`-O-H	83	85
trans-sinapinic acid 2`-O-H	78	78

The AIP parameter is related to the SET-PT mechanism. It describes the process of electron donation by the antioxidant. Molecules with low AIP values are more susceptible to ionization and have stronger antioxidant properties. The values of AIP have been presented in Table 2. For the *trans-p*-coumaric acid the AIP values are lower in water medium than in vacuum. This fact is related with electrostatic interaction of water medium with cation radical forms of the compounds. The AIP value for the *trans*-sinapinic acid is lower in vacuum than for *trans-p*-coumaric acids. Generally huge AIP values indicate that SET-PT is not te preferred antioxidant mechanism for these two molecules.

Table 2. AIP and PDE values [kcal/mol] calculated on B3LYP/6-311+G(2d,2p) level of theory

Compound	AIP		PDE	
	Vacuum	Water	Vacuum	Water
trans-p-coumaric acid	182	135	215	4
trans-sinapinic acid	172	104	220	2

The PDE parameter characterizes the second step of the SET-PT mechanism. PDE values are also presented in Table 2. The high values of this parameter in vacuum confirm that this mechanism is not preferred. The low values of the PDE parameter for the *trans-p*-coumaric acid in water indicates that this step is energetically favored for this compound in polar medium.

PA and ETE parameters are related with the SPLET mechanism (Table 3). The PA values for both investigated compounds are high in vacuum and small in polar medium. It favors the SPLET mechanism in polar medium for *trans-p*-coumaric and *trans*-sinapinic acids. The second parameter ETE is smaller for both compounds in vacuum than in water medium.

$\Delta H_{acidity}$ and $\Delta G_{acidity}$ are parameters related with the TMC mechanism. Values of $\Delta H_{acidity}$ are comparable for

Table 3. PA and ETE values [kcal/mol] calculated on B3LYP/ 6-311+G(2d,2p) level of theory

Bond	PA		ETE	
	Vacuum	Water	Vacuum	Water
trans-p-coumaric acid 2`-O-H	328	31	69	108
trans-sinapinic acid 2`-O-H	330	30	62	103

both studied molecules. The huge values of this parameter indicate that this mechanism is not preferred for those two compounds in vacuum. $\Delta G_{acidity}$ is connected with calculations performed in solvents. The huge value of $\Delta G_{acidity}$ demonstrates that the TMC mechanism is also not preferred in water medium.

Table 4. $\Delta H_{acidity}$ and $\Delta G_{acidity}$ values [kcal/mol] calculated on B3LYP/6-311+G(2d,2p) level of theory

Bond	$\Delta H_{acidity}$ (Vacuum)	$\Delta G_{acidity}$ (Water)
trans-*p*-coumaric acid 2`-O-H	326	291
trans-sinapinic acid 2`-O-H	328	290

On the basis of the performed computations we predict that for *trans*-*p*-coumaric and *trans*-sinapinic acids the most preferred mechanism in vacuum is HAT, and in water solution – SPLET.

III. 3. HOMO - LUMO distribution and SD

The energies of HOMO and LUMO are not antioxidant descriptors but can be connected to the antioxidant activity of molecules. Higher HOMO energies indicate better electron-donating properties of a molecule. The E_{HOMO} value of *trans*-*p*-coumaric acid is slightly lower than for the *trans*-sinapinic acid in vacuum as well as in water environment (Table 5). The electronic density of these orbitals in vacuum and in water medium is concentrated on

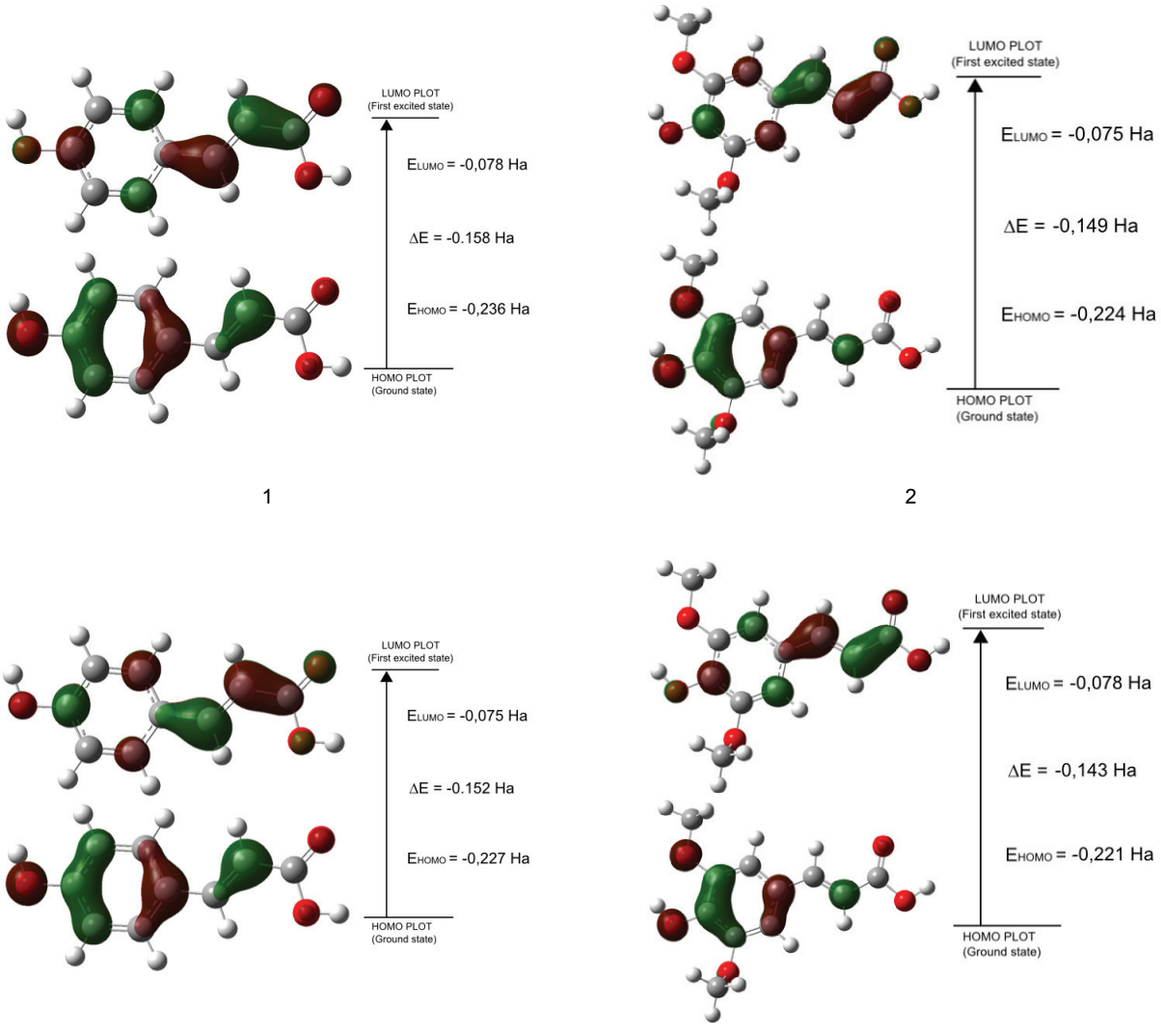

Fig. 6. The atomic orbital compositions of the frontier molecular orbital for *trans*-*p*-coumaric acid in vacuum (1) and in water medium (2) and for *trans*-sinapinic acid in vacuum (3) and in water medium (4)

Table 5. The HOMO energy (E_{HOMO}) of *trans-p*-coumaric acid and *trans*-sinapinic acid obtained on rB3LYP/6-311G+(2d,2p) level in vacuum and in water medium

Compound	Vacuum		Water	
	E_{HOMO} [Ha]	E_{HOMO} [eV]	E_{HOMO} [Ha]	E_{HOMO} [eV]
trans-p-coumaric acid	−0.236	−6.4	−0.227	−6.2
trans-sinapinic acid	−0.224	−6.1	−0.221	−6.0

Table 6. The LUMO energy (E_{LUMO}) of *trans-p*-coumaric acid and *trans*-sinapinic acid obtained on rB3LYP/6-311G+(2d,2p) level in vacuum and in water medium

Compound	Vacuum		Water	
	E_{LUMO} [Ha]	E_{LUMO} [eV]	E_{LUMO} [Ha]	E_{LUMO} [eV]
trans-p-coumaric acid	−0.078	−2.1	−0.075	−2.0
trans-sinapinic acid	−0.075	−2.0	−0.078	−2.1

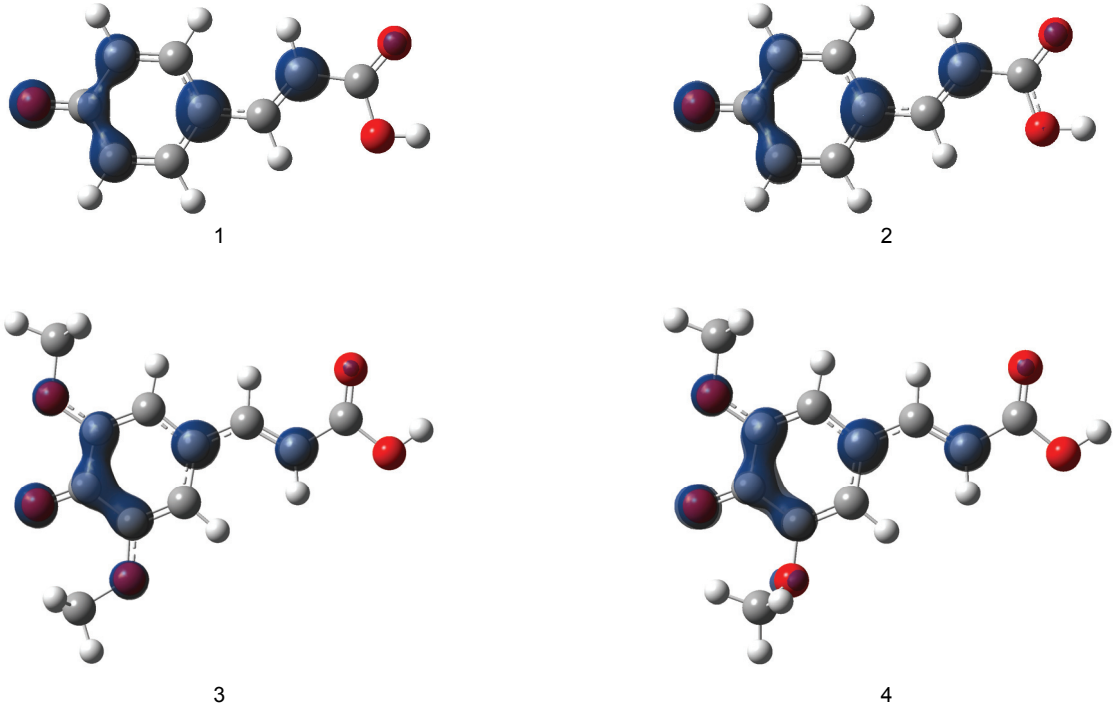

Fig. 7. The uB3LYP/6-311+G(2d,2p) SD distribution for 2`-O-radical of *trans-p*-coumaric acid in vacuum (1) and in water medium (2) and 2`-O-radical of *trans*-sinapinic acid in vacuum (3) and in water medium (4). The calculations were accomplished with isovalue 0.004

the oxygen from the hydroxyl group, phenyl ring and vinyl bond in the *trans-p*-coumaric acid (Fig. 6). In case of the *trans*-sinapinic acid the electron density concentrates on the oxygen from the hydroxyl group and methoxy groups, phenyl ring and vinyl bond (Fig. 6). It can be concluded that the O-H bond is the most probable place of a free-radical reaction in the whole molecule in the studied compounds. The energy difference between LUMO and HOMO orbital energies determines the chemical reactivity. This difference shows how easy the transition is from the ground to the excited state (Table 7 and Fig. 6), and how it is related to the stability of radical forms of molecules. Analysis of spin density in 2`-O-radicals of molecules studied shows huge spin density concentration on 2`-O atoms and carbon atoms in a vinyl bond (Fig. 7 and Fig. 8). Groups with high spin density concentration are sensitive to a free-radical attack.

Table 7. ΔE ($E_{LUMO} - E_{HOMO}$) calculated using rB3LYP/6-311G +(2d,2p) for *trans-p*-coumaric acid and ΔE for *trans*-sinapinic acid calculated in vacuum and in water medium

Compound	Vacuum		Water	
	ΔE [Ha]	ΔE [eV]	ΔE [Ha]	ΔE [eV]
trans-p-coumaric acid	0.158	4.3	0.152	4.2
trans-sinapinic acid	0.149	4.1	0.143	3.9

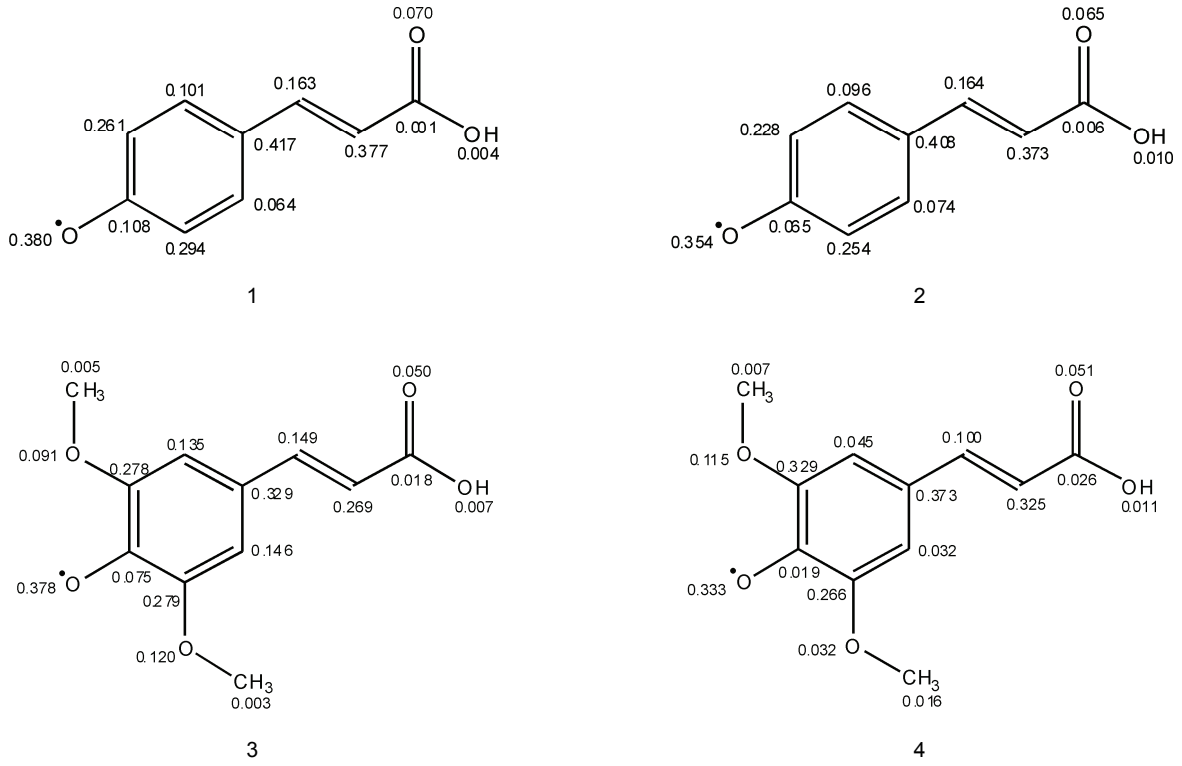

Fig.8. The uB3LYP/6-311+G(2d,2p) atomic SD values for 2`-O-radical of *trans-p*-coumaric acid in vacuum (1) and in water medium (2) and 2`-O-radical of *trans*-sinapinic acid in vacuum (3) and in water medium (4)

IV. CONCLUSIONS

Structure-antioxidant relationships of the *trans-p*--coumaric and *trans*-sinapinic acids have been investigated employing the DFT/B3LYP method together with the 6-311+G(2d,2p) basis set in vacuum and in water medium. Based on the obtained results we conclude that the O-H group is accountable for antioxidant abilities. We also suggest that for both investigated compounds the HAT mechanism is favored in vacuum whereas SPLET is favored in water medium. Quantum chemical calculations confirmed high antioxidant activity of both considered compounds.

Acknowledgements

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SUPPLEMENT

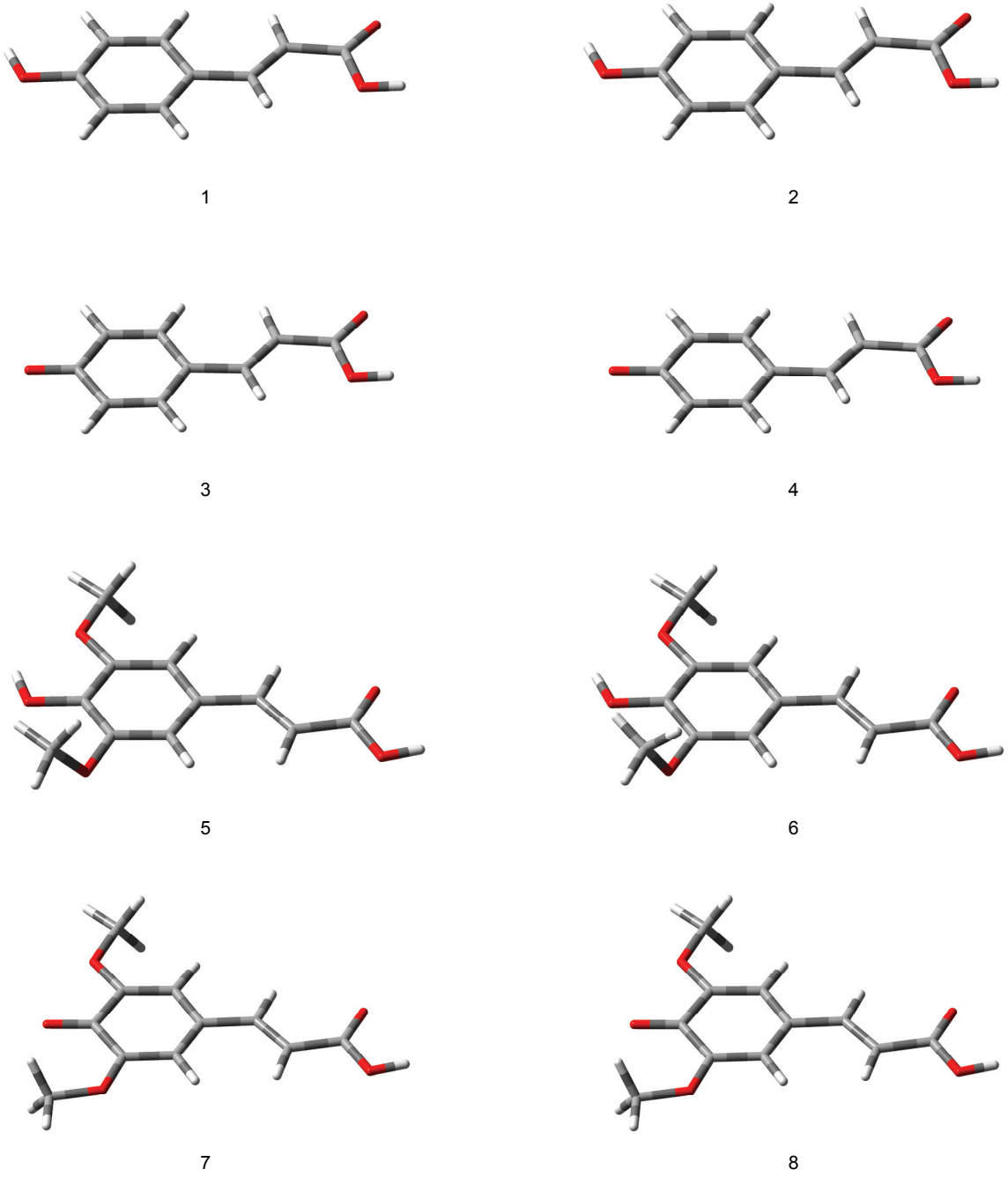

Fig. S.1. The B3LYP/6-311+G(2d,2p) optimized geometries of *trans-p*-coumaric acid in vacuum (1) and in water medium (2) and its 2`-O-radical form in vacuum (3) and in water medium (4) and *trans*-sinapinic acid in vacuum (5) and in water medium (6) and its 2`-O-radical form in vacuum (7) and in water medium (8)

ALICJA URBANIAK, PhD student in chemistry at Adam Mickiewicz University in Poznań. Received Msc degree in chemistry in 2012 at Adam Mickiewicz University in Poznań. Her scientific interests are: quantum chemical calculations of antioxidant properties of substances used in cosmetology.

MARCIN MOLSKI – associate professor at Theoretical Chemistry Department of Adam Mickiewicz University of Poznań. Degrees: PhD chemistry (1992), PhD in Physics (1997), Habilitation (2002). Publications: over 100 scientific papers and 3 books. The research interests concern, among other the following topics: quantum-mechanical determination of chemical, physical and biological properties of bio-active natural substances endowed with antioxidant properties, development of a quasi-quantum theory including macroscopic nonlocal and coherent effects, application of the chaos theory in modeling of biological growth, stimulus-response relationships and cognitive processes in life, behavioral sciences and beyond.

MAŁGORZATA SZELĄG – PhD student in the Department of Human Molecular Genetics at the Faculty of Biology, Adam Mickiewicz University in Poznan. She received her MSc degree in Biotechnology from UAM in Poznan. Her main areas of interest are: natural antioxidants, QM/MM modeling of interactions between inhibitors and proteins, application of quantum mechanics in drug development.