

On the Thermodynamics of antioxidant action of naturally occurring hydroxyderivatives of *cis*-cinnamic acid

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Abstract

Antioxidant activity represents one of the important features of phenolic acids, such as hydroxyderivatives of cinnamic acid. However, in the case of *cis*-cinnamic acid derivatives, corresponding thermochemistry data can be still considered scarce. This work is focused on the two most relevant mechanisms of primary antioxidant action in gas-phase, non-polar benzene and in aqueous solution. Reaction enthalpies describing thermodynamics of Hydrogen Atom Transfer (HAT) and Sequential Proton-Loss – Electron Transfer (SPLET) mechanisms were theoretically investigated using (SMD) M06-2X/6-311++G(d,p) method for *cis-ortho*-coumaric, *cis-meta*-coumaric, *cis-para*-coumaric, *cis-ferulic*, *cis-sinapic* and *cis-caffeic* acid and their carboxylate anions. The effect of carboxyl COOH group deprotonation on the thermodynamics of studied mechanisms was assessed for the three environments.

Keywords: Phenolic acid, DFT; hydrogen atom transfer; sequential proton-loss – electron transfer

1. Introduction

Naturally occurring phenolic acids can be divided into two groups, hydroxybenzoic acids and hydroxycinnamic acids. From the chemical point of view, these compounds have attached at least one OH group to aromatic ring. Hydroxyderivatives of cinnamic acid (Fig. 1), as well as other natural phenolic compounds, represent secondary plant metabolites. They are a part of human diet and show various beneficial biological effects (Heleno et al., 2015; Saxena et al., 2012).

Antioxidant (radical scavenging) activity of phenolic acids belongs to their most important effects. There are three generally accepted mechanisms of primary antioxidant action of phenolic compounds: (i) Hydrogen Atom Transfer (HAT), (ii) Single-Electron Transfer – Proton Transfer (SET-PT) and (iii) Sequential Proton-Loss – Electron Transfer mechanism (SPLET) (Galano et al., 2016). Due to the presence of carboxyl group, these compounds are weak acids with first pK_a values between 4.25 and 4.56 (Ozkorucuklu et al., 2009). Depending on conditions, phenolic acids can be partially or fully dissociated in aqueous solutions.

Deprotonation may affect the radical scavenging activity, as it was shown for various (poly)phenolic substances (Amić et al., 2018 and 2020; DiMeo et al., 2013; Estevéz et al., 2010; Klein et al., 2016; Lemańska et al., 2001).

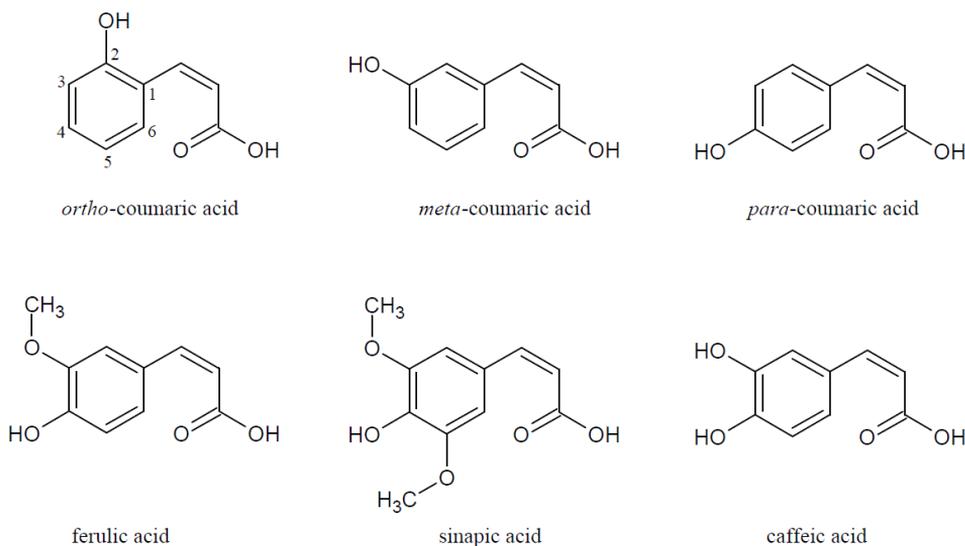
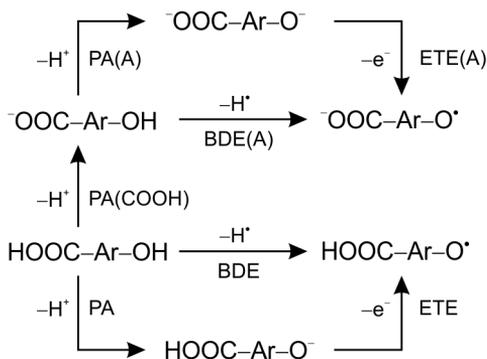
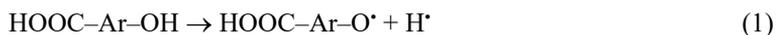


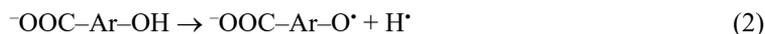
Fig. 1. Investigated derivatives of *cis*-cinnamic acid



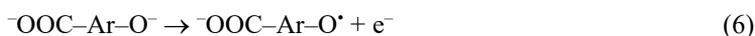
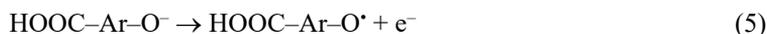
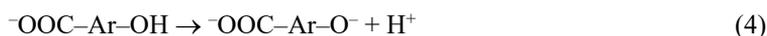
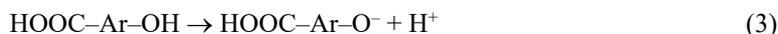
Scheme 1. Studied processes and denotations of reaction enthalpies

In nature, cinnamic acid derivatives are mainly present as *trans*-isomers, therefore most publications are focused on them (Amić et al., 2018; Chen et al., 2015; Koroleva et al., 2014; Mazzone et al., 2016). Thus, in this paper we decided to investigate the thermochemistry of homolytic and heterolytic cleavage of the phenolic O–H bonds of *cis*-cinnamic acid hydroxyderivatives (HOOC–Ar–OH) and their carboxylate anions (-OOC-Ar-OH). Our attention is focused on (i) HAT





and (ii) SPLET mechanisms (Scheme 1)



In eqs. 1–6, $\text{HOOC-Ar-O}^{\bullet}$ stands for phenoxy radical formed from parent non-dissociated acid, ${}^-\text{OOC-Ar-O}^{\bullet}$ is radical anion formed in HAT from carboxylate anion and ${}^-\text{OOC-Ar-O}^{-}$ represents the dianion with the two functional groups deprotonated. HAT and SPLET represent dominant pathways of phenolic antioxidants radical scavenging action (Amić et al., 2018 and 2020, Chen et al., 2015; DiMeo et al., 2013; Filipović et al., 2015; Klein et al., 2017; Lengyel et al., 2013; Marković et al. 2016, Škorňa et al., 2016a). According to our best knowledge, a comprehensive study of the thermodynamics of the two mechanisms in non-polar and polar aqueous environment for hydroxyderivatives of *cis*-cinnamic acid and their carboxylate anions is still missing. Therefore, the main aim of this work is to calculate relevant reaction enthalpies for parent acids and their deprotonated forms and analyze the effect of structural distinctions and environment affecting the thermochemistry of their primary antioxidant action. Following derivatives of *cis*-cinnamic acid were studied: *ortho*-coumaric acid, *meta*-coumaric acid, *para*-coumaric acid, ferulic acid, sinapic acid and caffeic acid (Fig. 1).

The next section of this report presents computational details. First part of Results and Discussion is focused on HAT mechanism for non-dissociated acids and the carboxylate anions in studied environments; the second part is devoted to SPLET mechanism. Based on obtained data, thermodynamically preferred mechanism is assessed for both, acids and their carboxylate anions. Finally, comparison of our results with available data is provided. In Conclusions, most important findings are summarized.

2. Computational details

Quantum chemical calculations were performed in Gaussian 09 program package (Frisch et al., 2013). Hybrid functional M06-2X recommended for calculations of thermochemistry of organic compounds (Zhao and Truhlar, 2008) was employed in this work. For all calculations, 6-311++G(d,p) basis set was employed (Hariharan and Pople, 1973; Rassolov et al., 1998). This basis set including diffusion and polarization functions provides reliable description of studied species. The energy cut-off was 10^{-5} kJ mol⁻¹ and final RMS energy gradient under 0.01 kJ mol⁻¹ Å⁻¹. Vibrational analysis confirmed that found species are in real energy minima (no imaginary frequencies). SMD (Solvation Model based on the quantum mechanical charge Density of a solute molecule interacting with a continuum) approach (Marenich et al., 2009) was used to compute solution-phase optimum geometries and the total enthalpies of studied species in benzene (mimicking non-polar environment) and water. From the total enthalpies of molecules, radicals, anions, radical anions and dianions, these reaction enthalpies (see Scheme 1 for used denotations) were determined

$$\text{BDE} = H(\text{HOOC-Ar-O}^{\bullet}) + H(\text{H}^{\bullet}) - H(\text{HOOC-Ar-OH}) \quad (7)$$

$$\text{BDE(A)} = H({}^-\text{OOC-Ar-O}^{\bullet}) + H(\text{H}^{\bullet}) - H({}^-\text{OOC-Ar-OH}) \quad (8)$$

$$\text{PA} = H(\text{HOOC-Ar-O}^{-}) + H(\text{H}^{+}) - H(\text{HOOC-Ar-OH}) \quad (9)$$

$$\text{PA(A)} = H(\text{-OOC-Ar-O}^-) + H(\text{H}^+) - H(\text{-OOC-Ar-OH}) \quad (10)$$

$$\text{PA(COOH)} = H(\text{-OOC-Ar-OH}) + H(\text{H}^+) - H(\text{HOOC-Ar-OH}) \quad (11)$$

$$\text{ETE} = H(\text{HOOC-Ar-O}^\bullet) + H(\text{e}^-) - H(\text{HOOC-Ar-O}^-) \quad (12)$$

$$\text{ETE(A)} = H(\text{-OOC-Ar-O}^\bullet) + H(\text{e}^-) - H(\text{-OOC-Ar-O}^-) \quad (13)$$

In eqs. 7–13, $H(\text{H}^+)$ is the calculated total enthalpy of the proton, $H(\text{H}^\bullet)$ is the total enthalpy of the hydrogen atom, and $H(\text{e}^-)$ is the total enthalpy of the electron. The gas-phase M06-2X/6-311++G(d,p) total enthalpy of the hydrogen atom is $-1301.81 \text{ kJ mol}^{-1}$, for solution-phase calculations the values of $-1305.81 \text{ kJ mol}^{-1}$ (water) and $-1295.41 \text{ kJ mol}^{-1}$ (benzene) were used. For proton and electron, following total enthalpies were used: $H(\text{H}^+, \text{water}) = -1049,80 \text{ kJ mol}^{-1}$, $H(\text{H}^+, \text{benzene}) = -864,80 \text{ kJ mol}^{-1}$, $H(\text{e}^-, \text{water}) = -73.86 \text{ kJ mol}^{-1}$, $H(\text{e}^-, \text{benzene}) = -10.86 \text{ kJ mol}^{-1}$ (Škorňa et al., 2016b). All thermodynamic quantities were computed for the temperature $T = 298.15 \text{ K}$.

3. Results and discussion

Carboxyl COOH group of investigated *cis*-derivatives of cinnamic acid can show two conformations: with carbonyl oxygen or OH group rotated towards the aromatic ring. The total enthalpies of the two conformers are similar, differences in the gas-phase do not exceed 7 kJ mol^{-1} . In benzene and water, found differences are within 6 and 2 kJ mol^{-1} , respectively. For all molecules, conformer with carbonyl oxygen oriented towards the aromatic ring shows lower total enthalpy (see the structure of *para*-coumaric acid in Fig. 2). Reaction enthalpies calculated for the products corresponding to the two conformations reached analogous values, i.e. in all environments, differences in BDEs and PAs for the two conformers are lower than 7 and 5 kJ mol^{-1} , respectively. This indicates that the orientation of COOH group does not play a considerable role. In further text and tables, reaction enthalpies for the conformer with lower total enthalpy are presented. In tables, the lowest value in each column is set in italic.

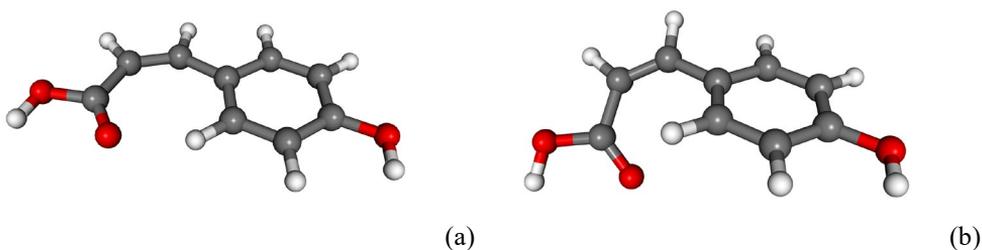


Fig. 2. Optimized structures of *cis-para*-coumaric acid in gas-phase (a) and water (b). Note that the side chain is not co-planar with aromatic ring in water.

In ferulic and sinapic acid, intramolecular hydrogen bond (IHB) between phenolic OH group and neighboring methoxy OCH_3 group is present. In caffeic acid, possessing *ortho*-dihydroxy (catechol) structure, $\text{O4-H}\cdots\text{O3}$ IHB is formed between the two OH groups. IHBs are responsible for an increase in O–H BDE and PA values, because the abstraction of H^\bullet or H^+ from the OH group participating in IHB requires its disruption, too. This effect is pronounced in gas-phase, in aqueous solution IHBs are considerably weaker (Michalík et al., 2019).

3.1. Hydrogen atom transfer mechanism

For parent, non-dissociated molecules, differences in gas-phase and solution-phase BDE values (Table 1) are within 9 kJ mol⁻¹ for OH groups which do not participate in intramolecular hydrogen bonds. With exception of *para*-coumaric acid, gas-phase BDEs are lower than those found for benzene and water environment. In ferulic acid, IHB formed between OH and OCH₃ groups, responsible for the rise in BDE, is compensated with the effect of OCH₃ group tending to decrease O–H BDE. Therefore, O–H BDE of ferulic and *para*-coumaric acids are in gas-phase and benzene practically identical. Only in water, the O–H BDE of ferulic acid is higher than the value found for *para*-coumaric acid and remains the same as in gas-phase and benzene. For sinapic acid, the decrease in BDE occurred in benzene (7 kJ mol⁻¹) and water (18 kJ mol⁻¹) in comparison to gas-phase. The presence of the additional OCH₃ group, placed in the second *ortho* position to OH group, results in the decrease in BDE. For caffeic acid with O4–H...O3 IHB, drop in BDE by 20 kJ mol⁻¹ was identified in water for 4-OH group. Due to considerably weaker IHB, the two OH groups have similar BDEs, while in gas-phase the difference between 3-OH and 4-OH BDEs is 33 kJ mol⁻¹. We note that 4-OH BDE does not reflect the subsequent rotation of 3-OH group to form new O3–H...O4 IHB stabilizing the radical.

Acid	BDE / kJ mol ⁻¹			BDE(A) / kJ mol ⁻¹		
	Gas	Benzene	Water	Gas	Benzene	Water
<i>cis-ortho</i> -coumaric	361	367	364	322	339	365
<i>cis-meta</i> -coumaric	367	372	368	374	377	376
<i>cis-para</i> -coumaric	368	368	362	<i>312</i>	<i>331</i>	360
<i>cis</i> -ferulic	367	367	368	320	332	344
<i>cis</i> -sinapic	356	349	<i>338</i>	331	339	<i>336</i>
<i>cis</i> -caffeic – 3-OH	<i>332</i>	<i>344</i>	341	336	341	347
<i>cis</i> -caffeic – 4-OH	365	369	345	327	337	344

Table 1. (SMD) M06-2X/6-311++G(d,p) BDE and BDE(A) values; the lowest value is in italic

For three coumaric acids, the position of OH group does not affect the BDE considerably. In the case of *ortho*-coumaric acid, the side chain attached to the aromatic ring at adjacent carbon atom causes steric hindrance resulting in OH group orientation away from the side chain. The side chain induces decrease in gas-phase BDE by 9 kJ mol⁻¹ in comparison to phenol with M06-2X/6-311++G(d,p) BDE = 370 kJ mol⁻¹ (Michalík et al., 2019). In the case of *meta*- and *para*-coumaric acids, gas-phase BDEs can be considered identical and they are higher than the value calculated for *ortho*-coumaric acid. In aqueous solution, *para*-coumaric acid shows the lowest BDE among the three acids. The environment and the position of OH group alter BDE in low extent, since all BDEs found for coumaric acids in Table 1 are in the narrow range of 11 kJ mol⁻¹.

The presence of 4-OH group is the only structural difference between caffeic and *meta*-coumaric acid. Second OH group induces significant decrease, 27–35 kJ mol⁻¹, in 3-OH BDE of caffeic acid. The largest effect can be observed in gas-phase and the lowest difference was identified in water. In gas-phase and benzene, 3-OH BDE of caffeic acid is the lowest one among all studied compounds. In aqueous solution, the lowest BDE value shows sinapic acid. However, its BDE is lower than 3-OH BDE of caffeic acid only by 3 kJ mol⁻¹.

The second part of Table 1 summarizes BDE(A) values calculated for carboxylate anions of investigated acids. Data in the table imply that COOH group deprotonation often causes drop in O–H bond dissociation enthalpy, i.e. BDEs are larger than BDE(A) values. As it could be

expected, the largest differences show gas-phase data. These are driven just by the electron structure of investigated species. For carboxylate anions in gas-phase, as well as in benzene, large decrease was identified for bond dissociation enthalpies of OH groups in *ortho* or *para* position to side chain, see values for *ortho*- and *para*-coumaric acid, ferulic acid and 4-OH group of caffeic acid. On the contrary, in all environments the rise in bond dissociation enthalpies, up to 8 kJ mol^{-1} , is observed for OH groups in *meta* position to the side chain, e.g. in *meta*-coumaric acid and 3-OH group of caffeic acid. Only in benzene, 3-OH BDE(A) for caffeic acid is lower by 3 kJ mol^{-1} than 3-OH BDE. Solvents attenuate the effect of the electron structure of studied species and BDE(A) values are closer to BDEs. In gas-phase, maximum difference of 55 kJ mol^{-1} was found for *para*-coumaric acid. In non-polar benzene, it is decreased to 35 kJ mol^{-1} .

For aqueous solution, maximum difference in BDE and BDE(A), 24 kJ mol^{-1} , shows ferulic acid. This acid shows large drop in O–H bond dissociation enthalpy upon deprotonation of COOH group in gas-phase (47 kJ mol^{-1}) and benzene (35 kJ mol^{-1}), too. For all other acids, deviations between BDE(A) and BDE values are within 8 kJ mol^{-1} . Low differences between BDE and BDE(A) in water were also found for non-dissociated and deprotonated flavonoids (Klein et al., 2016).

Interesting trend is observable in the case of *para*-coumaric, ferulic and sinapic acid. With increasing number of OCH₃ groups in *ortho* position, BDE(A) values in gas-phase and benzene are growing. However, in water, the presence of one or two OCH₃ groups results in the decrease in calculated BDE(A) values from 360 kJ mol^{-1} for *para*-coumaric to 336 kJ mol^{-1} for sinapic acid with the lowest BDE(A) among all studied carboxylate anions in water. This trend may be in relation with the different planarity of the carboxylate anions in aqueous solution. The side chain of *para*-coumaric acid anion can be considered co-planar with aromatic ring, only oxygen atoms of COO⁻ group are twisted out of the plane. In ferulic acid, whole side chain is twisted out of the aromatic ring plane. Thus, electron-withdrawing effect of COO⁻ group may be weaker due to lower conjugation between the side chain and the aromatic ring. In the case of sinapic acid, the steric hindrance between OCH₃ group and the side chain causes its considerable distortion from the planarity. Moreover, OCH₃ groups, as well as weaker IHB lead to further decrease in BDE(A) of carboxylate anions of ferulic and sinapic acid. Thus, sinapic acid with two OCH₃ groups has the lowest BDE(A) value in water. Water also affects partial charges of carbon atoms and oxygen atoms of COO⁻ group (data not shown). On the other hand, BDE(A) values show opposite trend in gas-phase and benzene. In the two environments, *para*-coumaric acid has the lowest BDE(A). Besides, compared to aqueous solution, carboxylate anions of ferulic and sinapic acids are more planar in gas-phase and benzene.

3.2. Proton affinities of carboxylate anions

Table 2 summarizes calculated proton affinities of carboxylate anions PA(COOH), i.e. reaction enthalpies of acid deprotonation. All PA(COOH) values can be found in narrow ranges: 27 kJ mol^{-1} in gas-phase, 17 kJ mol^{-1} in benzene and 4 kJ mol^{-1} in water. It confirms that substituents placed at aromatic ring do not affect the thermodynamics of COOH group deprotonation significantly, especially in aqueous solution. Data in Table 2 are in line with available experimental $\text{p}K_{\text{a}}$ values of *para*-coumaric, ferulic, sinapic and caffeic acid determined from capillary electrophoresis experiments by Ozkorucuklu et al. (2009). These are also in very narrow range from 4.25 to 4.34 with the estimated standard deviations from 0.03 to 0.06.

3.3. Sequential proton-loss – electron transfer mechanism

Calculated proton affinities compiled in Table 3 confirm that SPLET mechanism is thermodynamically favored in water representing polar ionization-supporting solvent. In water, proton affinities of phenolics are by ca one order lower than gas-phase values (Chen et al., 2015; Lengyel et al., 2013; Škorňa et al., 2016b; Urbaniak et al., 2013). However, gas-phase PAs enable to analyze the effect of the structure not affected by solvation induced changes. The lowest gas-phase PA was found for 3-OH group of caffeic acid with *ortho*-dihydroxy structure. The highest one shows *meta*-coumaric acid, where the effect of the side chain is weakest. On the contrary, OH group placed in the *para* position to side chain results in 41 kJ mol⁻¹ decrease in PA of *para*-coumaric acid. For *ortho*-coumaric acid, gas-phase PA is higher only by 6 kJ mol⁻¹ compared to *para*-coumaric acid. All gas-phase PAs lie in 44 kJ mol⁻¹ wide range. If one compares *para*-coumaric acid with ferulic acid possessing OCH₃ substituent in the *ortho*-position to phenolic OH group, formed IHB results in PA larger by 22 kJ mol⁻¹. The presence of the second OCH₃ group in sinapic acid leads to drop in PA. Difference between gas-phase values of ferulic and sinapic acids is 15 kJ mol⁻¹. Due to O4–H...O3 IHB in caffeic acid, 20 kJ mol⁻¹ difference between 3-OH and 4-OH PAs was found.

Acid	PA(COOH) / kJ mol ⁻¹		
	Gas	Benzene	Water
<i>cis-ortho</i> -coumaric	1422	439	112
<i>cis-meta</i> -coumaric	<i>1394</i>	<i>422</i>	<i>109</i>
<i>cis-para</i> -coumaric	1419	437	111
<i>cis</i> -ferulic	1422	437	112
<i>cis</i> -sinapic	1409	<i>422</i>	113
<i>cis</i> -caffeic	1395	429	111

Table 2. (SMD) M06-2X/6-311++G(d,p) PA(COOH) values; the lowest value is in italic

Acid	PA / kJ mol ⁻¹			PA(A) / kJ mol ⁻¹		
	Gas	Benzene	Water	Gas	Benzene	Water
<i>cis-ortho</i> -coumaric	1390	426	146	1695	569	157
<i>cis-meta</i> -coumaric	1425	455	157	1736	597	164
<i>cis-para</i> -coumaric	1384	<i>422</i>	146	<i>1682</i>	<i>561</i>	159
<i>cis</i> -ferulic	1406	439	148	1698	582	159
<i>cis</i> -sinapic	1391	427	146	1702	588	151
<i>cis</i> -caffeic – 3-OH	<i>1381</i>	426	<i>141</i>	1689	<i>561</i>	<i>148</i>
<i>cis</i> -caffeic – 4-OH	1401	443	147	1705	579	158

Table 3. (SMD) M06-2X/6-311++G(d,p) PA and PA(A) values; the lowest value is in italic

In benzene, PAs of studied acids are in 33 kJ mol⁻¹ wide range. In aqueous solution they lie in narrow 16 kJ mol⁻¹ range. If we do not consider the value of *meta*-coumaric acid in water, all PAs are in very narrow range from 141 to 148 kJ mol⁻¹ confirming that water significantly diminishes differences in PA caused by the structural features of investigated compounds. Analogously to gas-phase, the lowest PA was found for 3-OH group of caffeic acid, and the largest one for *meta*-coumaric acid. In benzene, the lowest PA was obtained for *para*-coumaric acid, however, the value of 422 kJ mol⁻¹ is close to the one for 3-OH group of caffeic acid (426 kJ mol⁻¹).

From the thermodynamics point of view, in gas-phase and non-polar benzene, HAT represents the preferred reaction pathway of non-dissociated phenolic acids. However, in agreement with other reports on phenolic acids (Amić et al., 2018; Chen et al., 2015; Urbaniak et al., 2013), SPLET represents favored mechanism in aqueous solution, because computed PAs are roughly three-times lower than BDEs.

Proton affinities PA(A) describing the thermodynamics of the first step of SPLET for phenolic OH groups of carboxylate anions are higher than PA ones, because the second deprotonation resulting in dianion formation is energetically more demanding. Data in Table 3 unambiguously confirm that this process can be feasible only in water. In gas-phase and benzene PA(A) values are higher by ca 300 kJ mol⁻¹ and 140 kJ mol⁻¹ than PA ones, respectively. On the other hand, average difference between PA(A) and PA values reached only 9 kJ mol⁻¹ in aqueous solution. Thus, deprotonation of carboxylic group has only a weak effect on the heterolytic dissociation of phenolic OH groups in water. All PA(A) values lie in 16 kJ mol⁻¹ range – the same range was found for PAs. Analogously to PAs, the lowest and the highest PA(A) values again reached 3-OH group of caffeic acid and *meta*-coumaric acid, respectively.

We can conclude that close PA and PA(A) values imply analogous tendency of non-dissociated parent acids and their carboxylate anions to enter SPLET mechanism in aqueous solution. Moreover, PA(A) values are still significantly lower than BDE(A) values. Therefore, in water SPLET remains thermodynamically favored reaction pathway also for carboxylate anions.

Table 4 summarizes electron transfer enthalpies for non-dissociated derivatives of *cis*-cinnamic acid and their carboxylate anions. Both, ETE and ETE(A) values are lowest in gas-phase and largest in aqueous solution. In some cases, opposite trends between the two reaction enthalpies of SPLET can be observed: molecules with high proton affinities show lower electron transfer enthalpies and *vice versa*. For example, gas-phase PA of *meta*-coumaric acid reached the highest value and its ETE is the lowest. This trend is related to the thermodynamic cycle if one considers that initial and final states are identical in HAT and SPLET mechanisms.

Acid	ETE / kJ mol ⁻¹			ETE(A) / kJ mol ⁻¹		
	Gas	Benzene	Water	Gas	Benzene	Water
<i>cis-ortho</i> -coumaric	283	360	401	-62	190	383
<i>cis-meta</i> -coumaric	252	339	394	-51	200	387
<i>cis-para</i> -coumaric	295	366	398	-58	189	375
<i>cis</i> -ferulic	273	348	402	-68	171	358
<i>cis</i> -sinapic	276	343	375	-60	170	359
<i>cis</i> -caffeic – 3-OH	262	338	382	-42	200	373
<i>cis</i> -caffeic – 4-OH	275	346	381	-66	178	361

Table 4. (SMD) M06-2X/6-311++G(d,p) ETE and ETE(A) values; the lowest value is in italic

From the comparison of ETE and ETE(A) in Table 4, it is evident that ETE(A) values are considerably lower than ETES in gas-phase and benzene. In gas-phase, ETE(A) values are even negative and the process is exothermic. This is again in direct relation to very high, ca 1700 kJ mol⁻¹, gas-phase PA(A) values, while PAs are by ca 300 kJ mol⁻¹ lower. On the other hand, BDEs are usually higher than BDE(A) values. This trend is observable also for benzene. PA(A) values are larger than PAs, therefore ETE(A) values are lower than ETES. Average differences reached 332 kJ mol⁻¹ and 163 kJ mol⁻¹ in gas-phase and benzene, respectively. In aqueous

solution, differences between PA and PA(A) values were not very pronounced. Thus, ETE(A) values and ETEs are also similar, with 19 kJ mol⁻¹ average difference.

3.4. Comparison of found results with published data

There are only two theoretical reports on *cis*-cinnamic acid derivatives (Koroleva et al., 2014; Urbaniak et al., 2013). Available B3LYP data for *para*-coumaric, ferulic and sinapic acid are compiled in Table 5. These show fair agreement with our data, though different computational approaches were employed. In general, B3LYP functional often underestimates BDE and gives remarkably lower values than M06-2X or M05-2X (Milenković et al., 2017; Marković et al., 2016; Marković and Tošović, 2016; Michalík et al., 2019; Škorňa et al., 2016b). Results of Koroleva et al. (2014) evidence that differences in gas-phase reaction enthalpies of HAT and SPLET computed for *cis*- and *trans*-cinnamic acid derivatives can reach tens of kJ mol⁻¹. Thus, found reaction enthalpies cannot be unambiguously confronted with results published for *trans*-isomers (Amić et al., 2018 and 2020; Chen et al., 2015; Marković and Tošović, 2016; Urbaniak et al., 2013). Unfortunately, there are no experimental reaction enthalpies of studied processes available. Only for non-substituted cinnamic acid, gas-phase acidity was recently determined in Dávalos et al. (2016). For (*E*)- and (*Z*)-cinnamic acid, PA(COOH) reached values of 1428 and 1416 kJ mol⁻¹, respectively. These are in line with M06-2X/6-311++G(d,p) values of studied derivatives in Table 2. In our previous work (Michalík et al., 2019), we have confirmed that employed computational approach provides reliable O–H BDEs of various mono-substituted phenols. Therefore, found reaction enthalpies of HAT and SPLET mechanisms may represent relevant prediction for investigated isomers of cinnamic acid derivatives.

Acid	Gas						Water		
	BDE	BDE(A)	PA	PA(A)	ETE	ETE(A)	BDE	PA	ETE
<i>cis-para</i> -coumaric	365 ^a	325 ^a		1676 ^a		-42.3 ^a			
<i>cis</i> -ferulic	324 ^a , 330 ^b	318 ^a	1400 ^b	1656 ^a	266 ^b	-42.3 ^a	338 ^b	128 ^b	335 ^b
<i>cis</i> -sinapic	330 ^a	294 ^a		1680 ^a		-77.6 ^a			

^a B3LYP/6-31++G(d,p) (Koroleva et al., 2014).

^b (C-PCM) B3LYP/6-311++G(2d,2p) (Urbaniak, et al., 2013).

Table 5. Published reaction enthalpies in kJ mol⁻¹ for gas-phase and aqueous solution

4. Conclusions

For six hydroxyderivatives of *cis*-cinnamic acid, reaction enthalpies of two radical scavenging mechanisms depicted in Scheme 1 were theoretically studied. Obtained (SMD) M06-2X/6-311++G(d,p) results indicate that in non-polar environment HAT is the preferred mechanism for both, acids and their carboxylate anions. Large enthalpies of COOH group deprotonation show that dissociation of studied acids may not play a considerable role in non-polar environment. In agreement with experimental reports, low proton affinities of carboxylate anions, PA(COOH), confirm that deprotonation of COOH group cannot be neglected in aqueous solution. In water, differences in reaction enthalpies computed for non-dissociated acids and their carboxylate anions are considerably lower compared to gas-phase or non-polar benzene environment. In the case of bond dissociation enthalpies, BDE and BDE(A), differences are within 8 kJ mol⁻¹. Only *cis*-ferulic acid shows BDE(A) considerably lower, by 24 kJ mol⁻¹, than BDE. As expected, PA(A) values are higher than PA ones. However, maximum difference does not exceed 13 kJ mol⁻¹ in water. Because PA(A) values are still

significantly lower than BDE(A) ones, in aqueous solution SPLET remains thermodynamically preferred pathway for the carboxylate anions, too. Although reaction enthalpies found for non-dissociated acids and corresponding carboxylate anions reached similar values in aqueous solution, we should note that antioxidant (radical scavenging) effect is also affected by kinetics of individual processes and other factors, e.g. the type of scavenged radical, the presence of other substances or various consecutive or concurrent reactions.

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References

- Amić A, Marković Z, Dimitrić Marković J M, Milenković D, Stepanić V (2020). Antioxidative potential of ferulic acid phenoxy radical. *Phytochemistry*, 170, 112218.
- Amić A, Marković Z, Klein E, Dimitrić Marković, J M, Milenković D (2018). Theoretical study of the thermodynamics of the mechanisms underlying antiradical activity of cinnamic acid derivatives, *Food Chem.*, 246, 481–489.
- Chen Y, Xiao H, Zheng J, Liang G (2015). Structure-thermodynamics-antioxidant activity relationships of selected natural phenolic acids and derivatives: An experimental and theoretical evaluation. *PLoS ONE*, 10, e0121276.
- Dávalos J Z, Lima C F R A C, Silva A M S, Santos L M N B F, Erra-Balsells R, Salum M L (2016). Energetics of neutral and deprotonated (*Z*)-cinnamic acid. *J. Chem. Thermodyn.*, 95, 195–201.
- Di Meo F, Lemaur V, Cornil J, Lazzaroni R, Duroux J-L, Olivier Y, Trouillas P (2013). Free radical scavenging by natural polyphenols: Atom versus electron transfer, *J. Phys. Chem. A*, 117, 2082–2092.
- Estevéz L, Otero N, Mosquera R A (2010). A computational study on the acidity dependence of radical-scavenging mechanisms of anthocyanidins, *J. Phys. Chem. B*, 114, 9706–9712.
- Filipović M, Marković Z, Đorović J, Marković J D, Lučić B., Amić D (2015). QSAR of the free radical scavenging potency of selected hydroxybenzoic acids and simple phenolics, *C. R. Chimie*, 18, 492–498.
- Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, et al. (2013). Gaussian 09, Revision D.01 Gaussian Inc, Wallingford, CT.
- Galano A, Mazzone A, Alvarez-Diduk R, Marino T, Raúl Alvarez-Idaboy J, Russo N (2016). Food Antioxidants: Chemical insights at the Molecular Level, *Annu. Rev. Food Sci. Technol.*, 7, 15.1–15.18.
- Hariharan P C, Pople J A (1973). The influence of polarization functions on molecular orbital hydrogenation energies, *Theor. Chim. Acta*, 28, 213–222.
- Heleno S A, Martins A, Queiroz M J R P, Ferreira I C F R (2015). Bioactivity of phenolic acids: Metabolites versus parent compounds: A review, *Food Chem.*, 173, 501–213.
- Klein E, Lukeš V, Rimarčík J, Kleinová A (2017). Theoretical study of primary antioxidant action thermodynamics. *J. Serbian Soc. Comput. Mech.*, 11, 130–138.

- Klein E, Rimarčík J, Senajová E, Vagánek A, Lengyel J (2016). Deprotonation of flavonoids severely alters the thermodynamics of the hydrogen atom transfer, *Comp. Theor. Chem.*, 1085, 7–17.
- Koroleva O, Torkova A, Nikolaev I, Khrameeva E, Fedorova T, Tsentlovich M, Amarowicz R (2014). Evaluation of the antiradical properties of phenolic acids. *Int. J. Mol. Sci.*, 15, 16351–16380.
- Lemańska K, Szymusiak H, Tyrakowska B, Zieliński R, Soffers A E M F, Rietjens I M C M (2001). The influence of pH on antioxidant properties and the mechanism of antioxidant action of hydroxyflavones, *Free Radic. Biol. Med.*, 31, 869–881.
- Lengyel J, Rimarčík J, Vagánek A, Klein E (2013). On the radical scavenging activity of isoflavones: Thermodynamics of O–H bond cleavage, *Phys. Chem. Chem. Phys.*, 15, 10895–10903.
- Marenich A V, Cramer C J, Truhlar D G (2009). Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions, *J. Phys. Chem. B*, 113, 6378–6396.
- Marković Z, Đorović J, Dimitrić Marković J M, Biočanin R, Amić D (2016). Comparative density functional study of antioxidative activity of the hydroxybenzoic acids and their anions, *Turk. J. Chem.*, 40, 499–509.
- Marković S, Tošović J (2016). Comparative study of the antioxidative activities of caffeoylquinic and caffeic acids. *Food Chem.*, 210, 585–592.
- Mazzone G, Russo N, Toscano M (2016). Antioxidant properties comparative study of natural hydroxycinnamic acids and structurally modified derivatives: Computational insights. *Comp. Theor. Chem.*, 1077, 39–47.
- Michalík M, Poliak P, Lukeš V, Klein E (2019). From phenols to quinones: Thermodynamics of radical scavenging activity of para-substituted phenols. *Phytochemistry*, 166, 112077.
- Milenković D, Đorović J, Jeremić S, Dimitrić Marković J M, Avdović E H, Marković Z (2017). Free Radical Scavenging Potency of Dihydroxybenzoic Acids. *J. Chem.*, 5936239.
- Ozkorucuklu S P, Beltrán J L, Fonrodona G, Barrón D, Alsancak G, Barbosa J (2009). Determination of dissociation constants of some hydroxylated benzoic and cinnamic acids in water from mobility and spectroscopic data obtained by CE-DAD, *J. Chem. Eng. Data*, 54, 807–811.
- Rassolov V, Pople J A, Ratner M, Windus T L (1998). 6-31G* basis set for atoms K through Zn, *J. Chem. Phys.*, 109, 1223–1229.
- Saxena M, Saxena J, Pradhan A (2012). Flavonoids and phenolic acids as antioxidants in plants and human health, *Int. J. Pharm. Sci. Rev. Res.*, 16, 130–134.
- Škorňa P, Michalík M, Klein E (2016a). Gallic acid: thermodynamics of the homolytic and heterolytic phenolic O–H bonds splitting-off, *Acta Chimica Slovaca*, 9, 114–123.
- Škorňa P, Rimarčík J, Poliak P, Lukeš V, Klein E (2016b). Thermodynamic study of vitamin B6 antioxidant potential, *Comp. Theor. Chem.*, 1077, 32–38.
- Urbaniak A, Szelağ M, Molski M (2013). Theoretical investigation of stereochemistry and solvent influence on antioxidant activity of ferulic acid. *Comp. Theor. Chem.*, 1012, 33–40.
- Zhao Y, Truhlar D G (2008). The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals, *Theor. Chem. Acc.*, 120, 215–241.