

# Topology Delimited Radical-Scavenging Propensity of Monohydroxycinnamic Acids

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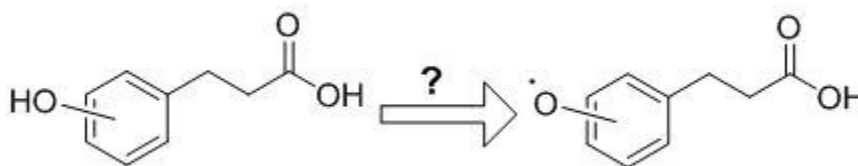
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## TOC graphic



The relationship between topology, geometry, electron and spin density distribution and the radical-scavenging activity is elucidated. Different mechanisms are discussed based on the enthalpies of the possible structures generated in the process of dissociation of the OH-bonds. All structures are modelled utilizing first principles methods and accounting for the polar medium at neutral pH. A hybrid mechanism is suggested applicable to phenolic acids in polar environment in polar environment.

## **Abstract**

Hydroxyl derivatives of cinnamic acid, both natural and synthetic, are well-known antioxidants. However, not all of them feature the same radical-scavenging propensity. Establishing the relation between structure and reactivity towards radical of those species plays a crucial role in the design of novel antioxidant pharmaceuticals founded on the same parent structure.

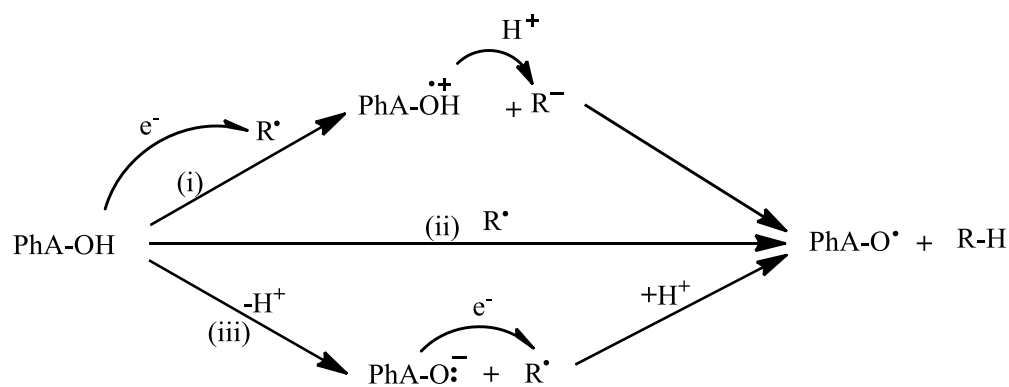
The study aims at clarifying the relationship between topology, geometry, electron and spin density distribution and the radical-scavenging activity. Different mechanisms are discussed based on the enthalpies of the possible structures generated in the process of dissociation of the OH-bonds. All structures are modelled utilizing first principles methods and accounting for the polar medium at neutral pH (B3LYP/6-311++G\*\*/PCM). A hybrid mechanism is suggested applicable not only to hydroxylated cinnamic acids but to phenolic acids in polar environment in general.

**Keywords:** molecular modelling, reaction mechanisms, topology, DFT/PCM, radical-scavenging

## Introduction

The interaction between the radical-scavenging cinnamic acids and reactive oxygen or nitrogen species can proceed via one of three basic mechanisms<sup>1-4</sup> (Scheme 1):

- (i) electron transfer from the antioxidant to the active radical, which produces a cation-radical and an anion; the electron transfer is followed by a proton transfer from the cation-radical to the anion (SET-PT);
- (ii) direct hydrogen atom transfer between the antioxidant and the active radical (HAT);
- (iii) deprotonation of the antioxidant followed by an electron transfer from the resulting anion to the active radical; the next step is protonation of the anion produced by the active radical (SPLET).



**Scheme. 1:** Mechanisms of the reaction between the radical-scavengers and active radicals.

Factors influencing the reaction pathway are the structure of the radical-scavenger, the redox potentials of the species involved, the environment (solvent) polarity, the temperature, etc.

The medium polarity is of major significance for the mechanism: in non-polar medium, HAT is the preferred route; with increase of environment's polarity, the mechanisms involving charged intermediates become more and more feasible.<sup>5</sup>

With radicals that are strong oxidizers, such as  $\text{Cl}_3\text{COO}\bullet$ , the mechanism beginning with an electron transfer may become the favoured one even in a non-polar medium.<sup>5</sup>

Ingold et al.<sup>6-13</sup> have shown that aprotic solvents slow down the reaction between phenolic radical-scavengers and active radicals. This is explained with the formation of hydrogen bonds with the aprotic solvent in which the phenolics act as proton donors from the OH-group, thus impeding the HAT mechanism. Only phenols that are not involved in H-bonds can react with radicals. The values obtained for the rate constants should depend on the strength of the H-bonds, on the solvent basicity,<sup>14</sup> and on the phenol acidity.<sup>15</sup> The presence of such a correlation evidences the proceeding of HAT mechanism, while its absence is a proof that the mechanism involves an electron transfer.<sup>13,16</sup>

Indeed, Litwinienko and Ingold have found<sup>17</sup> that the reaction between  $\text{ArOH} + \text{DPPH}\bullet$  in methanol and ethanol are faster than predicted and this is a proof for a non-HAT mechanism.

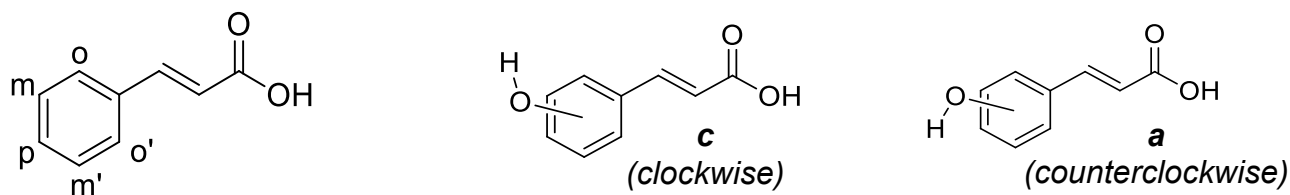
The stable  $\text{DPPH}\bullet$  radical is widely used for ‘assessment’ of the radical-scavenging/antioxidant potential of natural and synthetic phenolics. It is believed that ethanol and methanol are the most suitable solvents for this test.<sup>17</sup> The detailed mechanism of the interaction between the hydroxycinnamic acids and  $\text{DPPH}\bullet$  is still debatable as some contradicting results have been reported. Foti et al.<sup>18</sup> have found that the methyl esters of the sinapic, caffeic, and ferulic acids are more active than the acids themselves. Other authors<sup>19</sup> have established the same effect for the esters of the cinnamic acid, too. Yet, the same authors found the opposite effect for the esters of a dihydroxycinnamic acid – the esters were less active than the free acids.

The substantial enhancement of phenolic acids activity upon an increase of the medium pH has also been documented.<sup>20</sup>

To our knowledge, the role of the carboxyl group has not been discussed in any of the studies addressing the radical-scavenging properties of cinnamic acids. If its participation in the scavenging process in a non-polar environment (where the HAT mechanism is operative) can be neglected, this hardly will be the case in aqueous solution where heterolytic dissociations are anticipated to be dominant. All this motivated us to revisit the issue about the dependence of the radical-scavenging activity of hydroxycinnamic acids on their structure in aqueous medium with account of the contribution of the carboxyl group both as an electron-withdrawing moiety and as dissociable group producing a carboxylate anion and a proton.

## Computational Protocol

Scheme 2 shows the notations used to name the different isomers. All trans configuration of the side chain is presumed in all cases,<sup>21</sup> assuming that no isomerisation can occur during the radical-scavenging process. The two different orientations of the hydroxyl group are taken into account. Only the two ortho-isomers with hydroxyl groups oriented away from the side chain are considered (o-a and o'-c) because the other two (o-c and o'-a) are too unstable due to non-planarity disturbing the conjugation.



**Scheme 2:** Notations used for naming of the isomers.

The calculations were carried out using the DFT, as implemented in the Gaussian09 program package.<sup>22</sup> The optimization of the geometry was performed with the hybrid B3LYP functional utilizing the standard 6-311++G(d,p) basis set. No geometry constraints were applied. For all structures frequency analysis was made to confirm the true energy minima.

Solvent effects on the calculated structures were investigated with the self-consistent reaction field (SCRF) method, via the polarized continuum method (PCM).

The total enthalpies of the species X are usually estimated from the equation:

$$H(X) = E_0 + ZPE + \Delta H_{trans} + \Delta H_{rot} + \Delta H_{vib} + RT$$

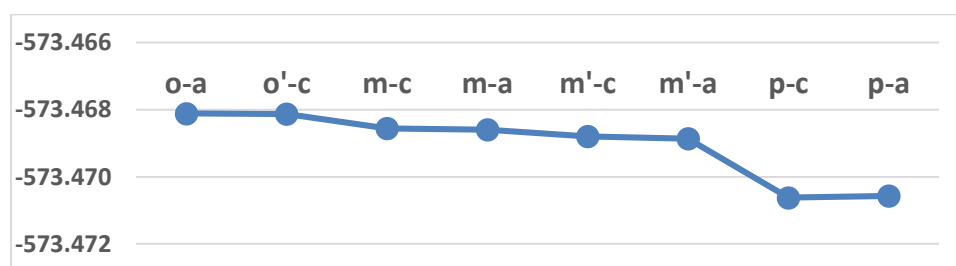
where  $E_0$  is the calculated total electronic energy, ZPE is the zero-point energy,  $\Delta H_{trans}$ ,  $\Delta H_{rot}$ , and  $\Delta H_{vib}$  are the translational, rotational and vibrational contributions to the enthalpy, RT represents the pV-work term added to convert the internal energy into enthalpy. The total enthalpies were calculated at  $T = 298$  K. The ZPE values were not scaled.

The enthalpies of the hydrogen atom, proton and electron in vacuum and in water are taken from the literature:<sup>23</sup> the used proton enthalpy ( $H_{(H^+)}$ ) in vacuum is 6.197 kJ/mol, and in water is  $-1083.803$  kJ.mol<sup>-1</sup>; the used enthalpy of an electron ( $H_{(e^-)}$ ) in vacuum is 3.145 kJ/mol, and in water is  $-232.676$  kJ.mol<sup>-1</sup>, the used enthalpy of a hydrogen atom ( $H_{(H\cdot)}$ ) in vacuum is  $-1312.479$  kJ/mol and in water is  $-1316.479$  kJ.mol<sup>-1</sup>. The updated enthalpy values for an electron and a proton in aqueous solution suggested by Markovic et al.<sup>24</sup> invoke no change in the trendlines established, so we will adhere to the values reported by Klein et al.<sup>23</sup> in order to allow comparison with earlier results on analogous systems.<sup>25</sup> Since the main objective of the paper is to reveal the structural origin of the radical-scavenging proclivity of the isomers, no comparison between the calculated and experimentally evaluated enthalpies is attempted.

## Results

### *BDE*

As expected, most stable is the para-isomer, irrespective of the orientation of the hydroxyl group hydrogen (*c* or *a*) due to the feasibility for electron density transfer to the carboxyl function. The remaining isomers are close in energy (within 2 kJ/mol), the ortho-isomers being slightly less stable due to stronger repulsion between the side chain and the proximate hydroxyl groups. As the charges on the  $\alpha$ - and  $\beta$ -C-atoms from the side chain are non-identical (the respective NBO group charges are -0.10 and +0.13, see Fig. S1; these values are conserved in all isomers), the Coulomb interactions with the substituents in the two ortho positions differ more prominently, which is felt, though milder even in the two meta sites. In other words, the perturbed symmetry of the molecule is the reason for the nonequivalent values of all parameters obtained for the o- and o'-species as well as for the m- and m' ones.



**Fig. 1:** Enthalpies (in a.u.) of the neutral monohydroxycinnamic acids. The points are connected in order to guide the eye

The numerical values show (Fig. 1, Table S2) that the meta-isomers have about 5 kJ/mol higher energy than the para-isomers, while the relative energies of the ortho-isomers are about 6.5 kJ/mol

higher than the para ones. The energies of m- and m'-species differ by less than 1 kJ/mol, while the two orientations of the hydroxyl group result in less than 0.2 kJ/mol difference for all parent isomers.

In order to explain the order of stability of the parent compounds (as well as their derivatives further on), we can make use of the charge distribution reflected in the dipole moments (Table 1).

**Table 1:** Dipole moments (in D) of the parent molecules in vacuum and in implicit water, their radical obtained after hydrogen abstraction from the hydroxyl group, and the cation radical obtained after an electron loss, the latter two in implicit water.

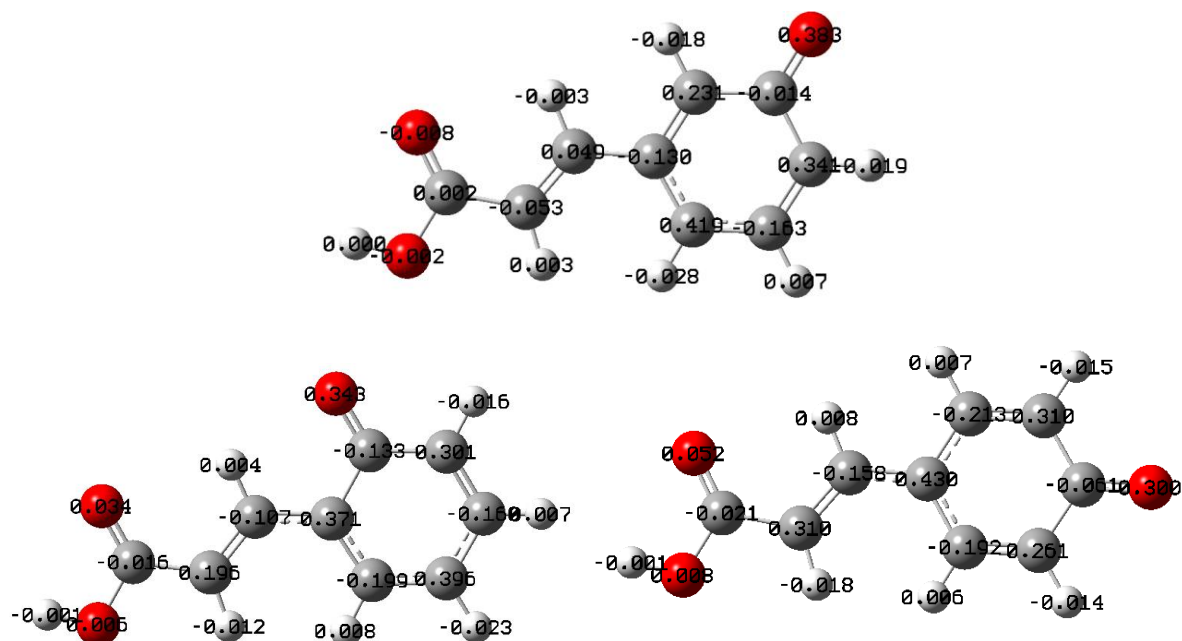
	<b>neutr_vac</b>	<b>neutral_wat</b>	<b>radical</b>	<b>cation-radical</b>
<b>o-a</b>	3.86	3.90	7.69	8.73
<b>o'-c</b>	4.22	4.31	5.47	9.30
<b>m-c</b>	1.23	1.28	6.30	7.86
<b>m-a</b>	3.91	3.96	6.30	11.37
<b>m'-c</b>	3.57	3.61	3.37	11.43
<b>m'-a</b>	1.93	2.01	3.37	8.03
<b>p-c</b>	3.06	3.16	4.58	7.99
<b>p-a</b>	3.72	3.84	4.58	8.36

The polarity of the molecule obviously depends on the topology and geometry of the hydroxyl group with respect to the side chain. The ortho and para positions allow electron transfer from the –OH to the –COOH group and this is reflected in the comparatively high dipole moments of these isomers both in vacuum and in water. The meta position obstructs electron density transfer and the dipole moment should be lower. Yet, the orientation of the hydroxyl hydrogen matters because



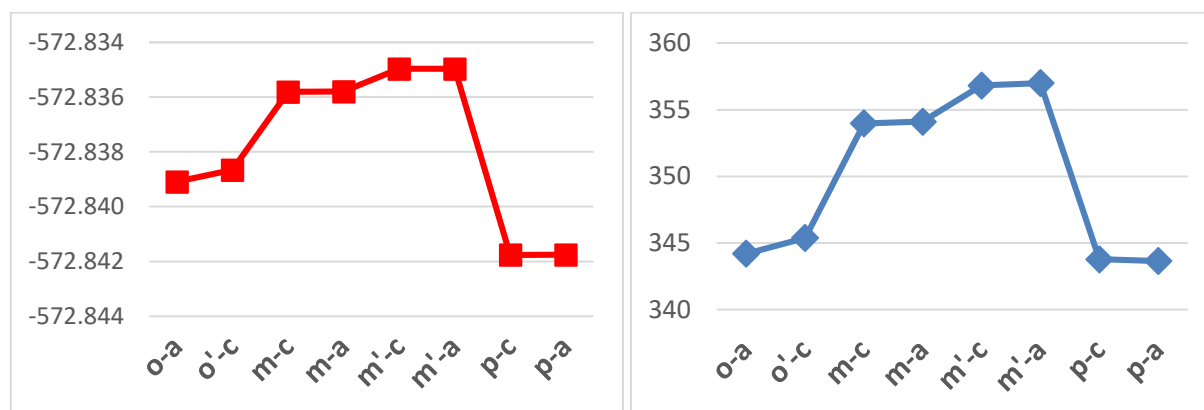
when the positively charged hydrogen points towards the negatively charged side chain (m-c, m'-a) the dipole moment decreases, whereas when it points to the opposite direction, the dipole moment increases (o-a, o'-c, m'-c, m-a). The water environment has additional polarizing effect resulting in almost all cases in an increase of polarity, though not in proportional manner. Thus, higher polarity seems to be a disadvantage, whereas good conjugation is favourable, so the combination of these explains the order of stability of the parent compounds.

The order of stability of the radicals obtained after abstraction of the hydroxyl hydrogen atom is dictated solely by the viability of electron density transfer between the two functional groups and the possibility for spin delocalization (Fig. 3). Therefore, the most stable are the radicals of the para isomers, followed by the ortho and meta ones. Here the energy differences are much more pronounced – the stability varies within about 18 kJ/mol; o and o' differ by 1 kJ/mol, while m and m' – by more than 2 kJ/mol (Fig. 2, Table S2).



**Fig. 2:** Mulliken spin densities in the radicals of meta- (top), ortho- (bottom left) and para- (bottom right) hydroxycinnamic acids, resulting from abstraction of the hydroxyl group hydrogen

The radicals' stability is a result of the interplay of electron density distribution and spin delocalization and polarization. Actually, the spin delocalization in organic radicals is achieved by means of spin polarization (alternation of spin density sign). In the radicals of all isomers the spin polarization is perfect (Fig. S2). However, the spin density value of the atom bonded to the side chain determines the extent of delocalization – the large values in the para and ortho radicals allow substantial spin delocalization in the side chain, largest in para and more moderate in ortho, while in the meta radicals the value is negligible and this prevents the stabilizing spin delocalization in the side chain, hence, the lower stability.



**Fig. 3:** Enthalpies (in a.u.) of the radicals obtained after homolytic fission of the OH-group (left, squares); enthalpy of homolytic dissociation (BDE in kJ/mol) of the hydroxyl group (right, diamonds). The points are connected in order to guide the eye.

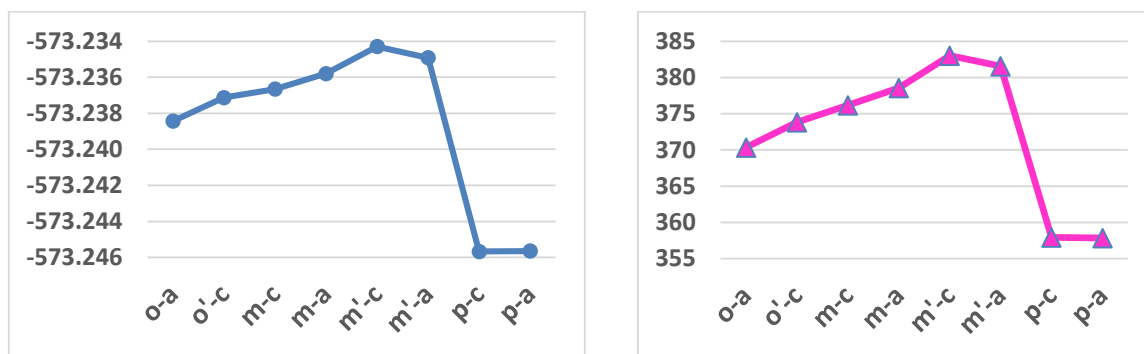
As the parent compounds are fairly close in energy, while the radicals differ markedly, it is not surprising that the BDE has almost the same profile as the radicals' stability. This demonstrates that the spin delocalization is critical for the decrease of BDE. Since the pattern of spin delocalization for the para and ortho isomers is essentially identical, the BDE values are also essentially identical (Table. S3). The bond dissociation enthalpy varies in the range  $BDE = 350 \pm 7$  kJ/mol, the values growing in the order  $p < o < m$ . The poor spin delocalization in the radicals of the

meta isomers (Fig. 2) is the reason that their BDE values are more than 10 kJ/mol higher (Table S3).

Hypothetically, a hydrogen atom could be abstracted also from the COOH group. However, the BDE of such an abstraction is by more than 70 kJ/mol higher ( $\text{BDE}_2 = 420 \pm 10 \text{ kJ/mol}$ , Table S3), which makes such a process absolutely unfeasible. Therefore, further on, our discussion about the preferred mechanism of radical-scavenging will consider the HAT mechanism represented solely by  $\text{BDE}_1$ .

## IP

We have already compared the stability of the parent compounds and the neutral radicals after hydrogen abstraction. In order to discuss the SET-PT mechanism, we first need to assess the stability of the cation-radicals obtained after electron loss from the parent isomers because this will determine the ionization potential.



**Fig. 4:** Enthalpy (in a.u.) of the cation radicals of the isomers (left) and ionization potential (in kJ/mol) of the parent molecules (right) The points are connected in order to guide the eye

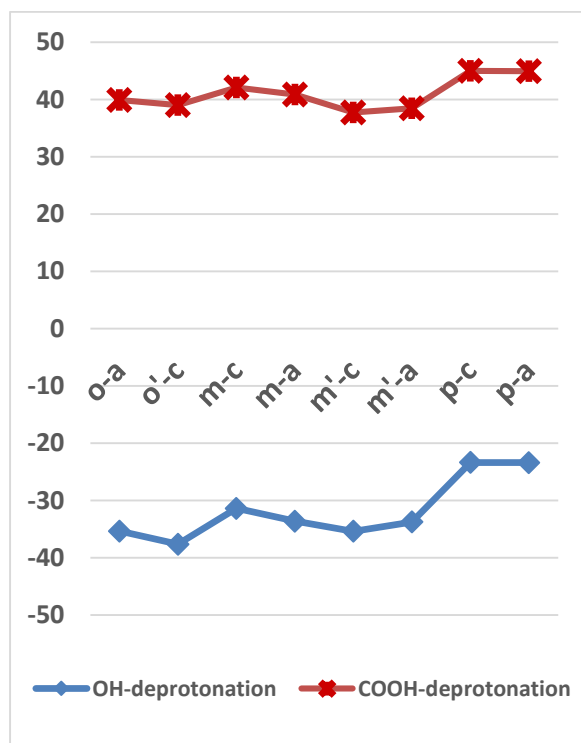
The order of stability of the cation-radicals is fairly similar to the radicals obtained from abstraction of the hydroxyl hydrogen, namely,  $m < o < p$ . However, there are several differences: Firstly, the

energy range is much larger – the enthalpy varies within about 30 kJ/mol, the ortho isomers being about 20 kJ/mol less stable than para, and the meta ones – 25-30 kJ/mol higher than para in enthalpy (Table S2, Fig. 4). Secondly, whereas the hydroxyl hydrogen is missing in the neutral radicals, *a* and *c* conformers with identical topology have the same energy, which is not the case with the cation-radicals – the orientation of the H-atom impacts the polarity and orientation towards the side chain reduces it, while direction away from the side chain increases it (Table 1, Fig. 4). Higher polarity results in higher reactivity (in heterolytic processes), which means lower stability, as evidenced in Table S2. In these cation-radicals, the difference in H-orientation invokes about 4 kJ/mol energy change, while the effect of the difference in topology (on the left or right to the side chain) is less pronounced – 2-3 kJ/mol. Thirdly, the spin polarization of the ortho and para isomers retains roughly the pattern of the neutral radicals. However, in the para isomers, the spin polarization is violated at a single site in the whole skeleton – only the carbon to which the –OH group is bonded has an inconsistent sign (Fig. S2). This, combined with the largest spin transfer between the two functional groups and with the mild polarity (Table 1), makes the para isomers the most stable. The ortho isomers exhibit a lower level of spin exchange and the meta ones – the lowest (Fig. S2); in addition, the spin polarization has two defects in the latter 6 isomers, which results in identical signs of the spin density at the oxygen termini, including in the 4 meta ones (unlike the neutral radicals). This makes the stability of the meta cation-radicals closer to that of the ortho ones. And finally, the spin polarization in the less polar meta structure is stronger and more efficient (Fig. S2) which is a favourable factor. The order of stability is biased again by the electron and spin density distribution – better spin polarization and delocalization and lower polarity being beneficial. Obviously, the spin density transfer from the hydroxyl to the side chain is the major factor for the radicals' stability.

The markedly larger differences in the enthalpies of the cation-radicals compared to the parent molecules make the IP profile practically identical to the cation radical one (see Fig. 4). On the other hand, the IP profile bears similarity to the BDE one (Fig. S3), which means that there is a certain proximity to the neutral radicals' profile.

### ***PDE***

Technically, there are two sites from which a proton can be removed from the respective cation-radical. Calculated values of the proton detachment enthalpy show that the O-H deprotonation is an exothermic process, whereas the proton detachment from the COOH group is endothermic (Fig. 5, Table S3). So, only the first process will be considered as a step in the heterolytic dissociation of the OH-group of the monohydroxycinnamic acids. Yet, it is remarkable that the two profiles are strictly parallel (Fig. 5).



**Fig. 5:** PDE from the OH- and from the COOH- group of the isomers. The points are connected in order to guide the eye

Essentially, PDE reflects the difference between the cation-radical and the neutral radical. Since the stability of the two types of radicals is governed by the same factors, the most stable cation-radical (para) should experience the least stabilization upon converting to neutral radical and this is exactly what the data show (Fig. 5, Table S2, S3). Among the remaining isomers, larger stabilization should occur when the deprotonation of the cation-radical results in a decrease of polarity and this is also supported by the calculated findings (Table 1, Table S2).

According to the postulate of Hammond,<sup>26</sup> which is the basis of this study, the transition states resemble structurally the closest in energy intermediates and products. We model the transition products of each stage. It follows from the Hammond postulate that if the enthalpy change in a certain stage is negative, this process will have a lower transition stage energy than the preceding stage, in which the enthalpy change is positive. In other words, from the variations of the thermodynamic functions along the reaction pathway, one can draw kinetics conclusions. Which means that rate determining is the stage with the largest positive enthalpy change.

The rate of proton abstraction from the hydroxyl group of the cation-radicals is not rate determining for the O-H bond dissociation. Rate determining is the electron detachment.

## ***PA***

PA, the descriptor for acidity, also does not characterize a rate determining process but it is worth mentioning that the obtained results adequately reflect the electron density shift towards the side chain. The fast proceeding of this stage directs the reaction along a specific pathway. There are two possible scenarios of deprotonation of the isomers – heterolytic dissociation of the carboxyl or of the hydroxyl group. As expected, the former is more favourable for the monohydroxycinnamic

acids. Yet, the resulting anions from the deprotonation of the ortho and para isomers are essentially isoenergetic (Fig. S4), which demonstrates the role of charge delocalization in these species.

Comparing the values of the group charges on the OH-group (Table S5), one can conclude that the higher the positive charge (the higher the polarity), the lower the stability. The same is true for the negative charge on the oxygen when the OH group is dissociated – the higher the negative charge on the oxygen, the worse the charge delocalization, the lesser the stability.

While the carboxyl group in the side chain enhances the acidity of the phenol groups (as the carboxyl group withdraws electron density), particularly those in the ortho and para position, for the same reason the hydroxyl groups in these positions reduce the carboxylic acidity.

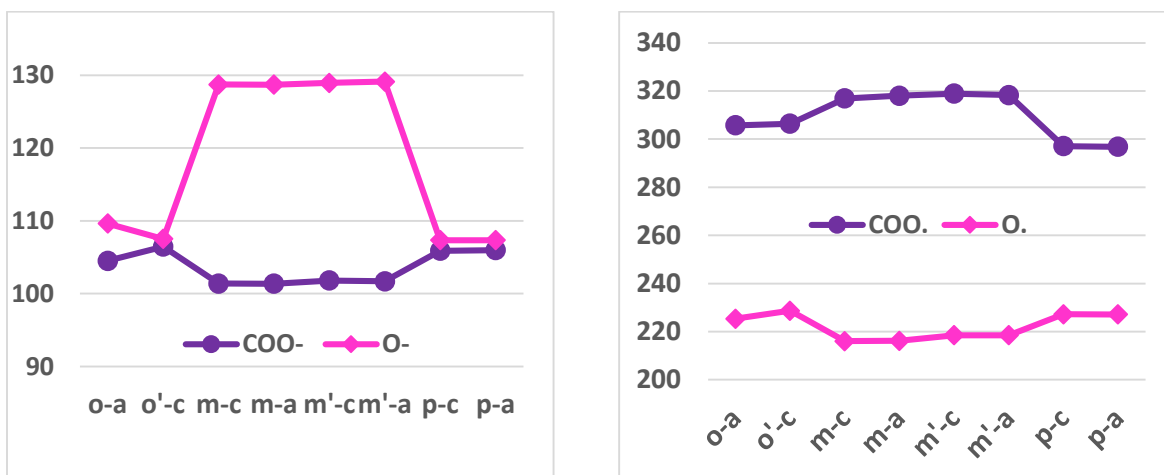
The energy profile of the anions obtained by dissociation of the COOH group resembles very much that of the parent compounds (Fig. 1, Fig. S4). This indicates that the deprotonation in the side chain does not change the order of stability. Comparing the values of the group charges on the OH-group (Table S5), one can conclude that the higher the positive charge (the higher the polarity), the lower the stability. The same is true for the negative charge on the oxygen when the OH group is dissociated – the higher the negative charge on the oxygen, the worse the charge delocalization, the lesser the stability.

The enthalpy change upon heterolytic dissociation of the carboxyl group is determined by the electron-donating behaviour of the hydroxyl group. Least dissociable are the acids, in which electron density from the hydroxyl group can be transferred mesomerically to the carboxyl one – the ortho and para isomers (Fig. 6, left). The impeded electron density shift in the meta isomers facilitates the carboxyl dissociation.

In contrast, the stability of the phenolate ions is enhanced by the charge delocalization. Therefore, as anticipated, the para phenolate ion is the most stable, closely followed by the ortho ones, while the meta ions are over 20 kJ/mol richer in enthalpy.

## ETE

Electron detachment from the anions obtained upon deprotonation of the parent isomers invokes different enthalpy changes. Much easier is the electron loss from the phenoxide ions, since the carboxylate ones are more stable than the latter (Fig. 6, right). The difference is of the order of 70 kJ/mol for para, 80 kJ/mol for ortho and 100 kJ/mol for meta species. Obviously, the more stable the anion, the lower the propensity towards electron loss (oxidation). It is easily seen that the profiles of ETE (Fig. 6, right) are strictly reverse to those of PA (Fig. 6, left). In any case, the oxidation of both types of anions is easier than the oxidation of the parent compounds – IP is higher than both ETE1 and ETE2.



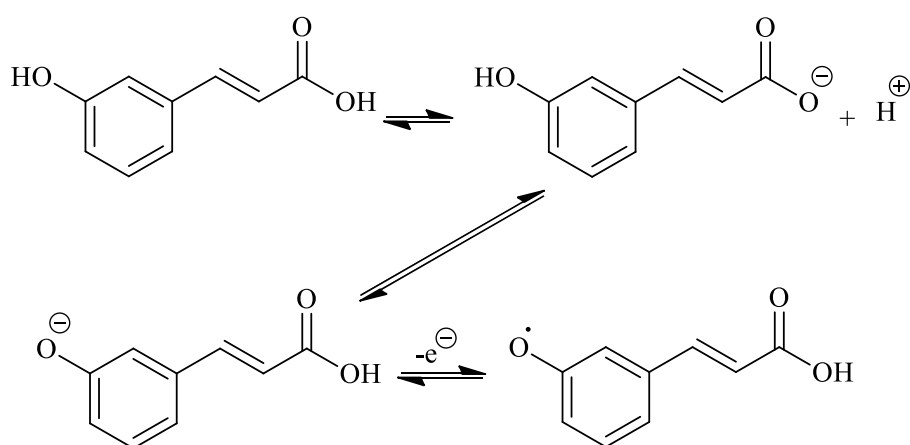
**Fig. 6:** PA (left) and ETE (right) values (in kJ/mol) of the anions obtained by deprotonation of the COOH group (circles) and the OH group (diamonds) of the parent isomers

Apparently, ETE is the rate determining step in the SPLET mechanism. In addition, it is the most favourable of the rate determining steps of all three mechanisms considered, even if we assume that both steps of the SPLET scenario involve only the carboxyl group. Yet, based on the values obtained, it can be hypothesized that after a fast dissociation of the carboxyl group, a proton



exchange occurs, so that subsequently the phenoxide ion is oxidized (Scheme 3). The proton exchange can proceed as an intramolecular, intermolecular or solvent-assisted process.

Such a mechanism probably will not speed up the reaction because it involves a three-step mechanism but could explain the difference in the kinetics of the hydroxycinnamic acids and their esters. On the other hand, the suggested scheme can explain why the antioxidant activity of meta-OH phenolic acids is comparable or even higher than the ortho ones.<sup>27-30</sup>



**Scheme 3:** Suggested mechanism of OH-dissociation in phenolic acids.

## Conclusion

All calculations are in implicit water environment, taking into account its polarizing effect. In such a medium, the most favourable in terms of enthalpy changes is the SPLET mechanism initiated by proton abstraction preferably from the carboxyl group, because this invokes smaller enthalpy changes. In the case of ortho and para isomers, this process can also occur from the hydroxyl group, as the enthalpy change is negligibly higher and the subsequent oxidation is substantially more favourable. For the meta isomers, however, deprotonation of the carboxyl group is imperative, because it is more acidic than the phenolic one. In the next stage, the meta anions may undergo

intra- or inter-molecular prototropy before or after their oxidation to radicals. A possible scheme of their scavenging performance is suggested (Scheme 3).

In general, SPLET is the major mechanism of OH-dissociation in the monohydroxycinnamic acids which typically has as initial step the deprotonation of the carboxyl group followed by a proton exchange resulting in the formation of a phenolate ion, which is further oxidized to a radical. The proton exchange seems to be particularly viable when the phenolate and carboxylate ions are close in energy as in the case of the ortho and para isomers. However, it would be most efficient for the meta-isomers which explains the sizeable antioxidant activity of various meta-OH phenolic acids.

## Acknowledgement

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## Conflict of interest

The authors declare no competing financial interest.

## Associated Content

**Supporting Information:** **Fig. S1:** NBO charges of cinnamic acid; **Fig. S2:** Spin density distribution in the cation-radicals; **Fig. S3:** Ionization potential vs. bond dissociation enthalpy; **Fig. S4:** Enthalpy of the anions obtained by deprotonation of the COOH group and the OH group; **Table S1:** Difference in the enthalpies of formation of the respective *cis* and *trans* isomers; **Table S2:** Enthalpy of the parent molecules, their radicals after the abstraction of the hydroxyl hydrogen atom, and their cation-radicals after electron loss; **Table S3:** BDE, IP and PDE; **Table S4:** PA and ETE; **Table S5:** Charges on the hydroxyl fragment upon deprotonation of the carboxyl and of the hydroxyl group.

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