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Different pathways of the *para*-O-H bond dissociation in di- and trihydroxyphenolic acids: a DFT investigation

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Phenols may inhibit but can also enhance oxidative damage processes in biomolecules. This ambivalent behavior heavily depends on their chemical structure. Phenolic acids with two and three hydroxyl groups and a different length and degree of saturation of the side chain are selected for this investigation. The radical-scavenging activity of the compounds was assessed, as well as the role of the different structural features on it. The most appropriate mechanism for the *para*-O-H bond breaking in an aqueous medium is determined. A high level DFT investigation was performed using the B3LYP functional with the 6-311++G(d,p) orbital basis; the solvent effects were evaluated by PCM.

Keywords: Phenols, DFT, Radical-scavenging, Reaction mechanisms

INTRODUCTION

The interest towards phenols is mainly determined by their antioxidant activity and by their involvement in the prevention of pathologies such as cancer [1,2], cardiovascular diseases [3-6] and inflammatory disorders [7]. The specific role of dietary and synthetic antioxidants in carcinogenesis is unclear [8]. The main proposed mechanism of this action is associated with the suppression of the harmful oxidative processes in the cells resulting from their radical-scavenging activity [6].

On the other hand, it has been found that some antioxidants, which may delay carcinogenesis, may also appear as accelerators of the tumor development in the second phase [9]. These compounds, depending on the concentration and type of active radicals, may also show pro-oxidative activity [10]. According to a suggested mechanism, the cytotoxicity of polyphenols may be due particularly to their prooxidant activity. Thus, depending on the structure, dose, target molecule, and environment, phenols may inhibit but also enhance oxidative damage processes in biomolecules [11], i.e. they can behave as anti- but also as pro-oxidants [10,12].

These controversial bioactivities of phenols depend heavily on their chemical structure [10,13,14]. It is believed that the prooxidant activity is proportional to the total number of hydroxyl groups in a flavonoid molecule [12]. Series of mono- and di-hydroxyflavonoids demonstrated no detectable prooxidant activity, while multiple hydroxyl groups, especially in the B-ring, significantly increased the production of hydroxyl radicals in the Fenton reaction [12,15].

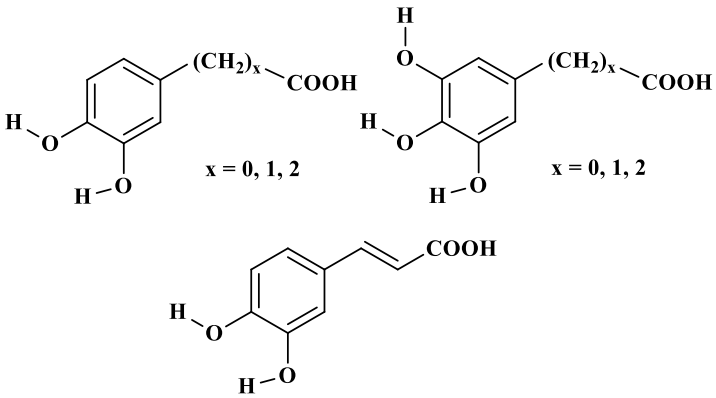

Figure 1. Structure of the investigated compounds

The target of this study is a series of phenolic acids (Figure 1) with: (i) two and three hydroxyl groups; (ii) different length and degree of saturation of the side chain [16]. What we will try to compare is the total reactivity of the phenolic compounds and specifically the reactivity toward radicals, related to the structural differences between them. Undoubtedly, the structural features have strong

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influence on the radical-scavenging activity [17]. Dissociation of the *para*-hydroxyl group *was* considered in the formation of phenoxyl radical presented in Figure 2.

The various phenolics react with active radicals following different mechanisms. This study should give an answer to the question which mechanism of the reaction between the investigated phenolic acids and radicals is preferred (Figure 2) [18-21]: (i) electron transfer from the antioxidant to the active radical, which produces a cation-radical and an anion; the electron transfer is followed by 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 electron transfer from the resulting anion to the active radical; the next step is protonation of the anion produced by the active radical (SPLET).

Some authors differentiate a fourth mechanism (iv) for the phenolic type antioxidants: proton-coupled electron-transfer (PCET) [19,22]. In the PCET mechanism, the radical (R•) possesses one or two lone pairs of electrons on the atom bearing the unpaired electron and the hydrogen transfer is mediated by an in-between formation of a temporary hydrogen bond which draws the O atom of PhA-OH and the radical center closer together, thus facilitating the proceeding of one of the above, e.g. the HAT, mechanism (see Figure 2). The mechanisms shown in Figure 2 address only the formation of the final stable radical PhA-O• and do not account for any subsequent transformations of this radical.

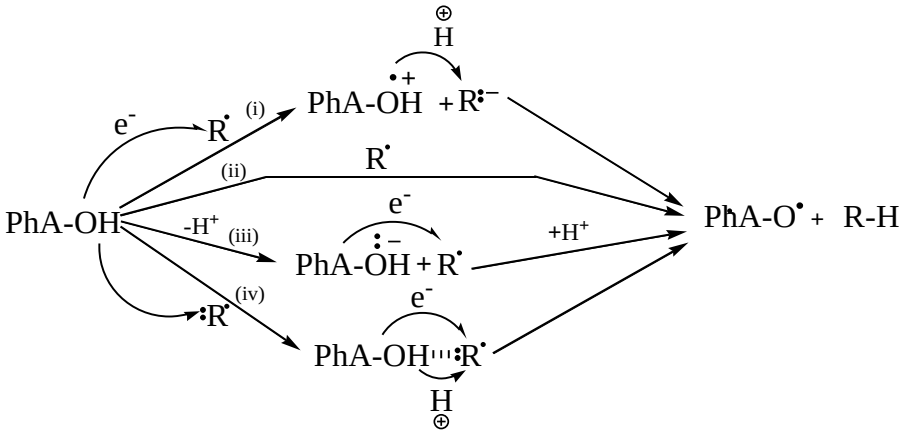

Figure 2. Mechanisms of O-H bond dissociation. PhA-OH stands for phenolic antioxidant.

The first step of mechanism (i) – Single Electron Transfer–Proton Transfer (SET–PT) can be described by the ionization potential (IP) or sometimes by the energy of the highest occupied molecular orbital according to Koopmans theorem [23,24]. As a rule, the second step is faster and can be quantified by the proton dissociation enthalpy (PDE) defined by equation 4. Mechanism (ii) Hydrogen Atom Transfer (HAT) dominates when the Bond Dissociation Enthalpy (BDE) is low (equation 2). Mechanism (iii): Sequential Proton Loss Electron Transfer (SPLET) is expected to occur only in antioxidants with an easily deprotonated functional group as the phenolics. SPLET is feasible when a hydroxyl group is acidic: the system features low proton affinity (PA) and low electron transfer enthalpy (ETE) as they are defined below (equations 5 and 6).

Normally, the free energy is the criterion for a thermodynamically preferred process. For the investigated reaction, Klein and co-authors have found that the absolute value of the entropic term ($T\Delta_r S$) is much smaller than the enthalpic term [25]. Therefore, a comparison of BDEs, IPs, PDEs, PAs and ETEs can show which mechanism is thermodynamically preferred. The utility of the values of enthalpy changes thus calculated is confirmed by their successful use in the QSAR analysis [26].

COMPUTATIONAL DETAILS

The calculations were carried out using the DFT, as implemented in the Gaussian09 program package [27]. The optimization of the geometry was performed with the Becke 3-parameter hybrid exchange functional combined with the Lee-Yang-Parr correlation functional (B3LYP) with the standard 6-311++G(d,p) basis set [28]. The optimization was achieved without any geometry constraints. For all structures the harmonic vibrational frequencies were computed to confirm the true minima on the calculated potential surface.

All possible intramolecular interactions were taken into account in the initial geometries.

Solvent effects on the calculated structures were investigated with the self-consistent reaction field

(SCRF) method, *via* the polarized continuum method (PCM) [29].

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

$$H(X) = E_0 + ZPE + \Delta H_{trans} + \Delta H_{rot} + \Delta H_{vib} + RT \quad (1)$$

where E_0 is the calculated total energy in the Born-Oppenheimer approximation, ZPE stands for the zero-point energy, ΔH_{trans}, ΔH_{rot}, and ΔH_{vib} are the translational, rotational and vibrational contributions to the enthalpy. Finally, RT is 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.

All calculated enthalpy changes are defined by equations *1–5*. From the calculated total enthalpies, we have determined the following quantities:

$$PhA\text{-}OH \leftrightarrow PhA\text{-}O^{\cdot} + H^{\cdot}$$

$$BDE = H_{(PhA\text{-}O\cdot)} + H_{(H\cdot)} - H_{(PhA\text{-}OH)} \quad (2)$$

$$PhA\text{-}OH \leftrightarrow PhA\text{-}OH^{\cdot+} + e^{-}$$

$$IP = H_{(PhA\text{-}OH^{\cdot+})} + H_{(e^-)} - H_{(PhA\text{-}OH)} \quad (3)$$

$$PhA\text{-}OH^{\cdot+} \leftrightarrow PhA\text{-}O^{\cdot} + H^{+}$$

$$PDE = H_{(PhA\text{-}O\cdot)} + H_{(H^+)} - H_{(PhA\text{-}OH^{\cdot+})} \quad (4)$$

$$PhA\text{-}OH \leftrightarrow PhA\text{-}O^{-} + H^{+}$$

$$PA = H_{(PhA\text{-}O^-)} + H_{(H^+)} - H_{(PhA\text{-}OH)} \quad (5)$$

$$PhA\text{-}O^{-} \leftrightarrow PhA\text{-}O^{\cdot} + e^{-}$$

$$ETE = H_{(PhA\text{-}O\cdot)} + H_{(e^-)} + H_{(PhA\text{-}O^-)} \quad (6)$$

The calculated proton enthalpy ($\mathbf{H_{(H^+)}}$) is -1083.803 kJ.mol^{-1}; the enthalpy of an electron ($\mathbf{H_{(e^-)}}$) is -232.676 kJ.mol^{-1}, the enthalpy of a hydrogen atom ($\mathbf{H_{(H^\cdot)}}$) is –1307.291 kJ.mol^{-1} [30].

Table 1. Enthalpy changes (in kJ/mol) related to the different mechanisms of O-H bond dissociation.

Compounds*	BDE	IP	PDE	PA	ETE
DHB	331.341	372.021	-49.868	98.733	223.421
DHPE	314.318	338.431	-33.301	97.237	207.894
DHPP	314.168	335.091	-30.111	102.870	202.109
DHPPE	315.433	341.358	-35.113	103.779	202.466
THB	311.907	370.606	-67.887	97.342	205.378
THPE	298.323	337.559	-48.424	97.024	192.112
THPP	295.267	331.996	-45.917	102.807	183.271

*Full names: 3,4-dihydroxybenzoic acid **(DHB)**, 3,4-dihydroxyphenyl ethanoic acid **(DHPE)**, 3,4-dihydroxyphenyl propanoic acid **(DHPP)**, *trans*-3,4-dihydroxyphenyl propenoic acid **(DHPPE,** caffeic acid**)**, 3,4,5-trihydroxybenzoic acid **(THB,** gallic acid**)**, 3,4,5-trihydroxyphenyl ethanoic acid **(THPE)**, 3,4,5-trihydroxyphenyl propanoic acid **(THPP)**.

RESULTS AND DISCUSSIONS

O-H Bond Dissociation Enthalpies (BDE)

The O-H BDE is indicative of the aptitude of a substance to enter into radical reactions and, therefore, for the radical-scavenging potential. Here we will only look at the change in the thermodynamic function associated with the detachment of the first hydrogen atom from the compounds because this is the rate-determining step. Subsequent cleavage of a hydrogen atom from the second (or third) hydroxyl group will result in the formation of a stable ortho-quinone.

However, BDE shows the ability to react with radicals only by the bimolecular one-stage mechanism (Figure 2, ii). The lowest BDE (under 300 kJ/mol) in an aqueous medium have the hydroxyl groups in THPP (295.267 kJ/mol) and in THPE (298.323 kJ/mol). Four of the investigated compounds have higher BDE values: THB (311.907 kJ/mol), DHPP (314.168 kJ/mol), DHPE (314.318 kJ/mol) and DHPPE (315.433 kJ/mol). As can be seen from Table 1, the highest BDE value stands for DHB (331.341 kJ/mol).

BDE decreases starting from acids with two hydroxyl groups to trihydroxyl acids in line with gradual elongation of the side chain. In other words, with side chain lengthening the ability to react with radicals increases and the trihydroxyl acids react more easily with radicals in a homolytic manner. The number of hydroxyl groups has a stronger impact on BDE than the chain extension.

Only the DHPPE deviates from this rule. This can be explained by the fact that the side chain in it is not saturated and links the mesomeric electron-withdrawing carboxyl group with the π-electronic system of the phenolic ring and the dissociable hydroxyl group at *para*-position.

The lower the BDE, the more reactive the compounds are. Also, the longer the chain and the greater the number of hydroxyl groups in the phenyl ring, the higher the reactivity of the acids with respect to radicals.

Ionization potential (IP)

IP is indicative for the propensity of the investigated compounds to participate in the SET-PT mechanism (Figure 1, i).

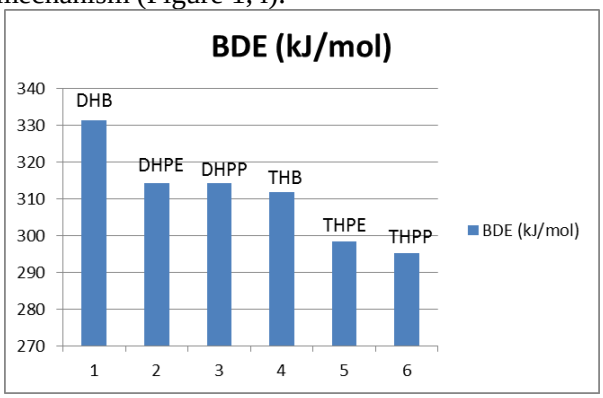

Chart 1. BDE dependence on the side chain length and the number of hydroxyl groups.

This is a two-stage mechanism that begins with an electron extraction from the phenolic acid and formation of a cation-radical followed by the cleavage of a proton. This mechanism (SET-PT), as well as the SPLET mechanism, is usually observed in the reactions between radical-scavengers and active radicals in polar solvents. Charged intermediates are formed in these mechanisms which are more stable in polar solvents.

BDE and IP have close values for every compound, but the latter are larger, which means that even in an aqueous environment the propensity to participate in a HAT mechanism is greater than in a SET-PT one.

The highest IP (and BDE) value possesses DHB (372.021 kJ / mol) and the lowest IP value has THPP (331.996 kJ / mol). Here, it should be noted again that the dihydroxyl derivatives have higher values than the trihydroxyl derivatives as it is with the BDE and again the positive inductive effect of the side-chain lowers the IP and increases the propensity of the compounds to react with the radicals in a SET-PT mechanism. Here, in contrast to BDE, the side chain length has a stronger impact on the IP than the number of hydroxyl groups.

The significantly higher IP values of the benzoic acid derivatives have to be explained separately. Generally speaking, the structural factors affecting the BDE affect the IP in a similar way. Only with THB and DHB the electron-withdrawing effect of the carboxyl group has a significantly stronger impact on the IP than on the BDE.

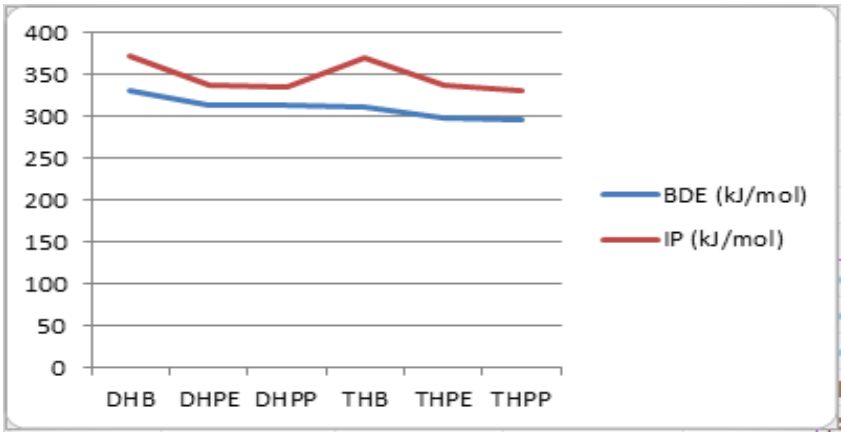

Chart 2. IP and BDE profiles.

Obviously, the direct bond between the phenyl ring and the carboxyl group allows the carboxyl group to have a negative mesomeric effect on the electron density in the phenyl ring, and this is the reason for the significantly higher enthalpy needed to detach an electron from benzoic acid derivatives. This is confirmed by the fact that the trihydroxyl derivatives (having one more electron-donating hydroxyl group) have a slightly lower ionization potential than the dihydroxyls (See Figure 1).

Proton dissociation enthalpies (PDE)

According to the SET-PT mechanism, an electron is initially torn off from the phenolic acids and a cation-radical is formed. Then a proton is cleaved from the cation-radical to form the corresponding radical, which is also produced by the other two mechanisms (Figure 2). PDE shows the propensity of the cation-radicals of phenolic acids to give up protons and become radicals [49]. PDE values indicate that proton cleavage is an exothermic process. This is an energy-efficient process and the rate of the reaction will depend solely on the electron detachment rate. The PDE can serve only as a measure of the acidity of the OH groups of the cation-radicals of the phenolic acids and for the acids themselves.

As can be seen, this is the only descriptor that has negative values. The most acidic is the hydroxyl

group at the para-position of the cation-radical of THB, followed by the para-hydroxyl group in the cation-radical of the DHA.

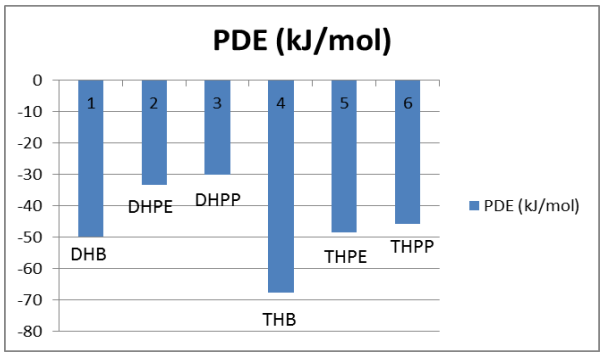

Chart 3. Acidity of the cation-radicals of the phenolic acids studied.

The least acidic are the hydroxyl groups in DHPP and DHPE. Again, DHPPE occupies a special place in the group of compounds under consideration. Here again, the negative mesomeric effect of the carboxyl group in DHB and THB, as well as the side chain induction effect in the other compounds influence the acidity. The rate of electron detachment will be determining for the total reaction rate in the SET-PT mechanism (Fig. 2 (i)).

Proton affinity (PA)

PA, the enthalpy of proton dissociation from the carboxyl group of the phenolic acids, is another measure of their acidity. It can be seen from the table that the highest acidity possesses THPE (97.024 kJ/mol) and immediately after it are DHPE (97.237 kJ/mol), THB (97.342 kJ/mol) and DHB (98.733 kJ/mol). Roughly, the remaining acids have close PA values: THPP (102.807 kJ/mol), DHPP (102.870 kJ/mol) and DHPPE (103.779 kJ/mol). The lowest acidity has DHPPE (103.779 kJ/mol).

Surely, the detachment of a proton from the acid is not a rate-determining step in the SPLET mechanism. ETE is indicative of the ability of the anion to release an electron. The removal of an electron from the anion of THPP (183.271kJ/mol) is the easiest because it requires the least amount of energy. The removal of an electron from the anion of DHB (223.421 kJ/mol) is the most difficult. This is not surprising. Generally, electron separation from more stable anions is more difficult. Therefore, the more difficult process in the SPLET-mechanism is the detachment of an electron.

Electron transfer enthalpies (ETE)

Ultimately, it turns out that the SPLET mechanism will be implemented in the aqueous environment. The rate that can be achieved with this mechanism will be significantly higher than the remaining mechanisms if the reaction occurs in an aqueous environment.

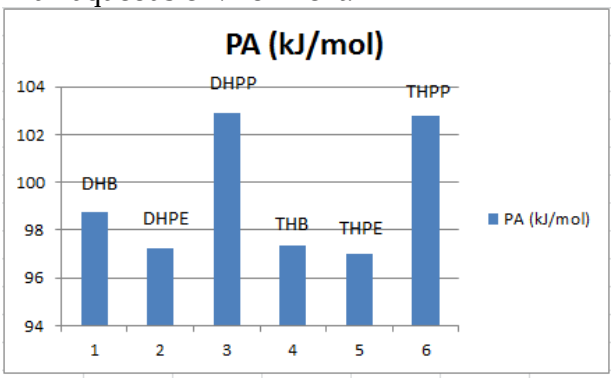

Chart 4. Proton affinity of the investigated phenolic acids.

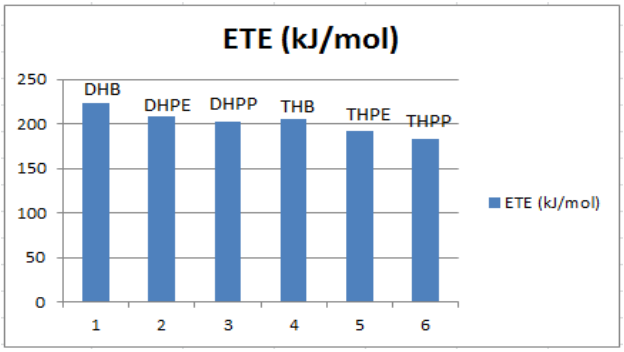

Chart 5. Enthalpy of the electron release from the phenolic anions.

CONCLUSION

❖ The study made it clear that the most active compound is THPP, followed by THPE, while DHB has the lowest activity against radicals.

❖ The trihydroxyl derivatives give away a hydrogen atom more easily than the dihydroxyl derivatives. The trihydroxyl derivatives, with the exception of THB, release an electron more easily. They are also stronger radical-scavengers than the dihydroxyl derivatives.

❖ The elongation of the hydrocarbon chain leads to an enhancement of the radical-scavenging activity. THB and DHB are among the least reactive compounds.

❖ The obtained results reveal that SPLET is the determining mechanism of O-H bond dissociation in the target molecules. It passes through the most energetically stable intermediates

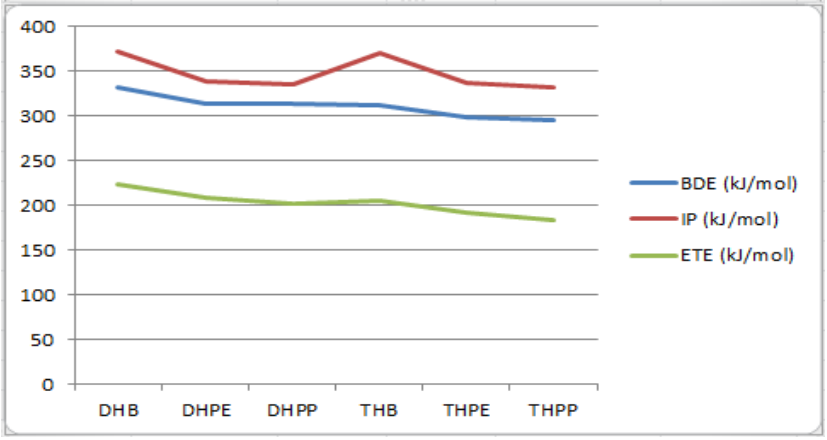

Chart 6. Comparison between BDE, IP, and ETE.

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РАЗЛИЧНИ ПЪТИЩА НА ДИСОЦИАЦИЯТА НА ПАРА-О-Н ВРЪЗКАТА В ДИ- И ТРИ-ХИДРОКСИФЕНОЛНИ КИСЕЛИНИ: DFT ИЗСЛЕДВАНЕ

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(Резюме)

Фенолите могат както да инхибират, така и да засилят оксидативните нарушения в биомолекулите. Това двойствено отнасяне силно зависи от химичната им структура. Обект на това изследване са фенолни киселини с две и три хидроксилни групи и различна дължина и степен на насищане на страничната верига. Оценени са радикал-улавящата активност на съединенията, както и влиянието върху нея на различните структурни характеристики. Определен е най-подходящият механизъм за разкъсване на пара-О-Н връзката във водна среда. Проведено е DFT изследване на високо ниво с използване на B3LYP функционал в комбинация с 6-311++G(d,p) орбитален базис. Влиянието на разтворителя е оценено чрез PCM.