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# Comparative density functional study of antioxidative activity of the hydroxybenzoic acids and their anions

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**Abstract:** Hydroxybenzoic acids (HBAs) and their anions play an important role in the food and pharmaceutical industries because of their antioxidant activity. In this study, we examined the mechanisms of the free radical scavenging action of HBAs and their anions using density functional theory (DFT) methods. Reaction enthalpies related to the mechanisms of free radical scavenging by the investigated species were calculated by DFT methods in water, DMSO, pentylethanoate, and benzene. Hydrogen atom transfer (HAT) is a preferred reaction pathway in benzene, while sequential proton loss electron transfer (SPLET) is a predominant reaction pathway in polar solvents, water, and DMSO for all species. For anions of HBAs, HAT and SPLET mechanisms in pentylethanoate are competitive, while SPLET is the most probable pathway in the case of HBAs.

**Key words:** Hydroxybenzoic acids, HAT, BDE, SPLET

## 1. Introduction

Hydroxybenzoic acids (HBAs) (Figure 1) are phenolic compounds for which there is evidence that they have many biological properties such as antiviral, anti-inflammatory, antioxidative, anticarcinogenic, and antibacterial activities. It should also be emphasized that there are experimental data for their physiological activity.[1] HBAs have been found in legumes (pea, bean, lentils), vegetables (carrots, asparagus), cereal grains (rye, wheat, buckwheat, soybean, oats), oilseeds (canola, mustard), and other plant species.[2–4] These compounds exist in free, glycosidic, and esterified forms in food of plant origin.[5,6]

Derivatives of HBAs are often used in human nutrition as a mixture of extracts of different plants.[7] For example, because of their biological and antioxidative activities, alkyl esters of *para*-hydroxybenzoic acid have often been used as preservatives in foods, cosmetics, beverages, and pharmaceuticals.[8] On the other hand, with the increasing length of the alkyl chain, the toxicity of phenolic compounds increases. Therefore, different esters of *para*-hydroxybenzoic acid such as methyl, ethyl, and propyl have been suggested for application as safe food and drug preservatives.[9] The maximum daily intake of *para*-hydroxybenzoic acid is 0.42 mg/kg.[10]

Application of these compounds in the chemical and food industries as well as in the pharmaceutical industry is closely related to their acidity since it is well known that there is a correlation between physical,

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chemical, and biological properties of organic compounds and their acidity. Keeping all this in mind, and the fact that at physiological pH 7.4 the number of deprotonated hydroxybenzoic acid molecules is significant, it is therefore required to examine the antioxidant properties of both acids and anions.[11]

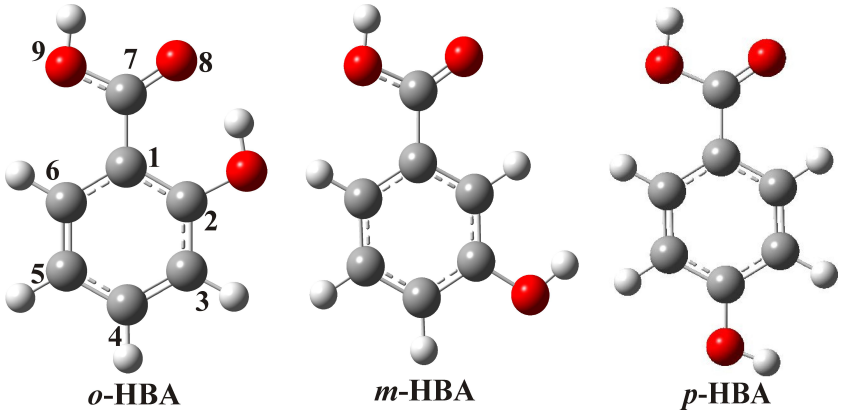


**Figure 1.** Structural formulas of hydroxybenzoic acids with atom labeling indicated.

The relationship between the structure and antioxidative properties of HBAs and their anions has not been fully elucidated yet. The mechanism of their antioxidative action and the action of the corresponding anions with different radicals in polar and nonpolar solvents has been investigated in one of our previous papers.[12] In this work, the mechanisms of the antioxidative action of HBAs and the corresponding anions are considered using standard thermodynamic parameters.

The antiradical capacity of HBAs is directly related to their ability to release phenolic hydrogen atoms. The newly resulting free radical is more stable and less reactive than the previous one. There are three generally accepted mechanisms of phenolic antioxidant action, namely hydrogen atom transfer (HAT):[13–16]

$$\mathrm{HBAO-H} \rightarrow \mathrm{HBAO^{\bullet}} + \mathrm{H^{\bullet}} \tag{1}$$

then single-electron transfer followed by proton transfer (SET-PT):

$$\mathrm{HBA-OH} \rightarrow \mathrm{HBA-OH^{\bullet+}} + \mathrm{e^{-}} \tag{2}$$

$$\mathrm{HBA-OH^{\bullet+}} \rightarrow \mathrm{HBA-O^{\bullet}} + \mathrm{H^{+}} \tag{3}$$

and sequential proton loss electron transfer (SPLET) mechanism:[16–20]

$$\mathrm{HBA-OH} \rightarrow \mathrm{HBA-O^{-}} + \mathrm{H^{+}} \tag{4}$$

$$\mathrm{HBA-O^{-}} \rightarrow \mathrm{HBA-O^{\bullet}} + \mathrm{e^{-}} \tag{5}$$

The net result of all three mechanisms is the same, i.e. the formation of the corresponding phenoxyl radical. Depending on reaction conditions, one of the possible mechanistic pathways may prevail under certain conditions. Experimental data related to all three mechanisms: HAT, SET-PT, and SPLET, are still missing. For this reason, the main goal of this work was to calculate the reaction enthalpies for all three HBAs using the DFT/M05-2X method. These enthalpies will be denoted as follows:

BDE – bond dissociation enthalpy related to Eq. (1); IP – ionization potential, enthalpy of electron transfer from the antioxidant molecule, Eq. (2); PDE – proton dissociation enthalpy, related to Eq. (3); PA – proton affinity of phenoxide ion, Eq. (4); ETE – electron transfer enthalpy, Eq. (5).

The present study also aimed to estimate the solvent effect of water, DMSO, pentylethanoate (PE), and benzene on individual reaction enthalpies. The importance of the polarity of solvents for SET-PT and SPLET mechanisms is emphasized, because of the ionic particles formed during these reactions. The mechanisms of HBAs' antioxidative action have already been investigated using the B3LYP method.[21−24] However, the SPLET mechanism has not been investigated so far. Moreover, the mechanisms of the antioxidative action of the HBA anions were investigated for the first time by means of thermodynamic parameters, as well as the influence of solvent polarity. In this study the hybrid GGA B3LYP-D2 and meta-GGA M05-2X functionals were used with the aim to better describe the short- and medium-range interatomic interactions. The SPLET mechanism was also investigated.

## 2. Results and discussion

All calculated reaction enthalpies for all HBAs and corresponding anions are collected in Tables 1 and 2. For each molecule and the corresponding anion, the lowest value of BDE, PDE, PA, and ETE is shown in italics. It should be pointed out that these theoretical results, based on reaction enthalpies of HBAs, are in agreement with experimental values for kinetic solvent effects on free radical scavenging ability of different phenolic compounds.[25] These theoretical results are in accordance with other DFT-predicted mechanisms, also based on thermodynamic calculations.[21−23] The BDE values of 396 and 395 kJ mol$^{-1}$ for *o*-HBA, and 369 and 370 kJ mol$^{-1}$ for *p*-HBA in water and benzene[23] are in good agreement with the B3LYP-D2 results. On the other hand, the IP values of 714 and 569 kJ mol$^{-1}$ for *o*-HBA, and 728 and 580 kJ mol$^{-1}$ for *p*-HBA in benzene and water[23] are in good agreement with the M05-2X results. The other values refer to the gas phase and have higher values for BDE, especially those obtained at the B3LYP/6-311++G(2d,2p) 6d level of theory. The IP values in the gas phase are significantly higher, over 800 kJ mol$^{-1}$.[21,22]

### 2.1. Reaction enthalpies of HBAs

The preferred antioxidative mechanism of HBAs can be predicted on the basis of BDE, IP, and PA values. Actually, the lowest of these thermodynamic values indicate which mechanism is preferable under certain conditions. Reaction enthalpies of three HBAs and corresponding anions were calculated using both DFT methods (Tables 1 and 2).

With careful analysis of the thermochemical data for BDE values presented in Table 1, it may be noted that 3-OH and 4-OH groups have greater potential to donate a H-atom. The results obtained by both methods show that m-OH has the lowest BDE value in all solvents, representing the first site that can donate its H-atom, followed by p-OH and o-OH groups. It is important to mention that all BDE values obtained by the B3LYP-D2 method are generally smaller by more than 20 kJ mol$^{-1}$. The main reason lies in the fact that, in comparison to DFT methods, DFT-D2 methods reproduce chemical reaction energies more accurately.[26] The results regarding the first oxidation site of HBAs, obtained by M05-2X, are also in good agreement with the results obtained by other authors like Mandado et al. and Hoelz et al.[21,22] It should also be pointed out that BDE values (in water and benzene) obtained by B3LYP-D2 are in good agreement with the corresponding values reported by Nenadis and Tsimidou obtained using the B3LYP/6-311++G (2d,2p)//B3LYP/6-31G model.[23]

**Table 1.** Calculated parameters of antioxidant mechanisms for HBAs in kJ mol$^{-1}$.

| | M05-2X | | | | | B3LYP-D2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *HAT* | *SET-PT* | | *SPLET* | | *HAT* | *SET-PT* | | *SPLET* | |
| | BDE | IP | PDE | PA | ETE | BDE | IP | PDE | PA | ETE |
| Water | | | | | | | | | | |
| *o-HBA* | 401 | *551* | 31 | 149 | 433 | 383 | *496* | 38 | 152 | 381 |
| *m-HBA* | *383* | 552 | 12 | 146 | *418* | *363* | 498 | 16 | 148 | *366* |
| *p-HBA* | 392 | 565 | *9* | *133* | 441 | 370 | 508 | *13* | *134* | 387 |
| Pentylethanoate | | | | | | | | | | |
| *o-HBA* | 407 | *620* | 52 | 292 | 380 | 387 | *589* | 49 | 287 | 351 |
| *m-HBA* | *374* | 626 | 12 | 274 | *365* | *354* | 594 | 11 | 267 | 338 |
| *p-HBA* | 380 | 638 | *7* | *250* | 395 | 358 | 603 | *7* | *244* | 366 |
| DMSO | | | | | | | | | | |
| *o-HBA* | 403 | *594* | –37 | 128 | 429 | 382 | *549* | –31 | 132 | 386 |
| *m-HBA* | *373* | 597 | –70 | 111 | *416* | *353* | 552 | –63 | 114 | *375* |
| *p-HBA* | 381 | 607 | *–72* | *91* | 443 | 359 | 559 | *–64* | *94* | 401 |
| Benzene | | | | | | | | | | |
| *o-HBA* | 412 | *694* | 127 | 458 | 363 | 392 | *675* | 106 | 434 | 348 |
| *m-HBA* | *374* | 702 | 81 | 437 | *346* | *355* | 683 | 62 | 411 | *333* |
| *p-HBA* | 379 | 713 | *75* | *410* | 378 | 358 | 690 | *58* | *384* | 364 |

The PA values of all HBAs obtained in all solvents and by both methods give the following sequence: 4-OH < 3-OH < 2-OH. These results indicate that proton transfer from the 4-OH group is easier in comparison to the other two OH groups. The PA values calculated for *o*-HBA and *p*-HBA in methanol are much higher than the corresponding values calculated for the other polar solvents (water and DMSO, Table 1).[23] It is not possible to verify the validity of the obtained results due to the absence of theoretical and experimental data for these solvents.

The IP value of HBAs is calculated as the difference between the enthalpy of HBAs radical cation and parent molecules in all solvents. The IP values are somewhat higher in nonpolar solvents than in polar ones. This is a consequence of additional stabilization of the radical cation in polar solvents. It may be noted that IPs depend on the position of the OH group in the ring. Thus, the lowest IP goes for HBA with a hydroxyl group situated in *ortho* position. It can be also noted that IP values obtained using M05-2X and-B3LYP-D2 methods are significantly lower compared to the values calculated by B3LYP/6-311++G(2d, 2p)//B3LYP/6-31G in water.[24] The reason probably lies in the fact that Nenadis and Tsimidou did not use the energy of electron in the formula for calculating the IP value.

The net result of the antioxidative action of HBAs by any mechanism is the corresponding radical. Figure 2 presents SOMOs and spin densities obtained by NBO analyses of the formed radicals. Both SOMO and spin density successfully represent delocalization of the unpaired electron and stability of phenoxyl radical.[24] The unpaired electron is delocalized over the oxygen, where the formation of free radicals takes place, and *ortho* and *para* carbon atoms. Figure 2 shows that spin density is better delocalized in polar solvents (water) and that the *ortho* radical is better delocalized in both solvents. The resonance effect is also responsible for the stabilization of the radical species. The radical form with more resonance structures is more stable and therefore *ortho* and *para* radicals are more stable than ones in *meta* position. As can be seen from Figure 2, *ortho* and *para* radicals have one resonance structure more, which provides extended electron delocalization including a carboxyl group.

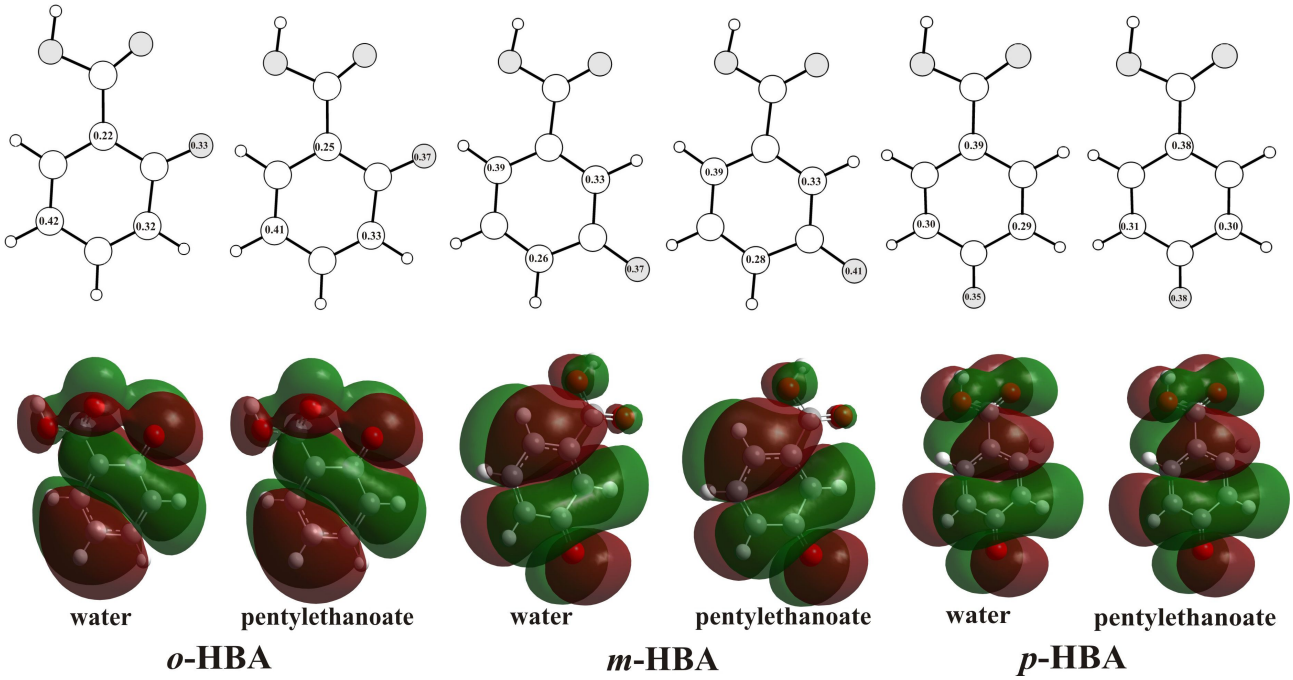


**Figure 2.** The spin density distribution (top) and SOMOs (bottom) of the radicals of hydroxybenzoic acids.

### 2.2. Reaction enthalpies of HBA anions

Thermochemical data for BDE values indicate that 3-OH and 4-OH groups of HBA anions have significantly greater potential to donate a H-atom than 2-OH (Table 2). The *p*-OH has the lowest BDE value in nonpolar solvents, while in polar solvents there is competition between 4-OH and 3-OH groups. The main reason for the significantly higher values of the BDE of the *o*-OH group is the formation of a considerably stronger hydrogen bond between the hydrogen of *o*-OH and carboxylate anion.

The PA values of all HBA anions show that *p*-OH has the lowest value in all solvents used. Just like with the BDE value, the PA value of the *o*-OH group is also significantly higher than the other two PA values. This is also a consequence of the formation of a strong hydrogen bond between the OH group and carboxylate anion. Obtained PA values in benzene, similarly to those obtained for HBA, are unexpectedly higher than in other solvents. On the other hand, there is no such pronounced difference between BDEs in the studied environments. The order of reactivity of OH groups is the same as in the case of HBAs.

The IP values of HBA anions are calculated as the difference between the enthalpy of HBA anions and HBA radicals in all solvents. The IP values of monoanions are generally lower than the corresponding values for HBAs, which is a consequence of the lower HOMO–LUMO gap of the anions compared to molecules. As in the case of HBAs, IP values depend on the position of the OH group in the ring; therefore, the *o*−HBA anion has a lower IP value than the other two anions in all solvents.

The final products of the antioxidative action of HBAs' anions by HAT, SPLET, and SET-PT mechanisms are the corresponding radical anions. The corresponding SOMOs and spin densities obtained by NBO analyses of formed radical anions are presented in Figure 3. The free radicals are delocalized, as well as in the case of HBAs, over the oxygen of the reactive OH groups and *ortho* and *para* carbon atoms. Figure 3 also shows that the spin density is better delocalized in polar solvents (water) and that the *ortho* radical is better delocalized

**Table 2.** Calculated parameters of antioxidant mechanisms for monoanion of HBAs in kJ mol$^{-1}$.

| | M05-2X | | | | | B3LYP-D2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *HAT* | *SET-PT* | | *SPLET* | | *HAT* | *SET-PT* | | *SPLET* | |
| | BDE | IP | PDE | PA | ETE | BDE | IP | PDE | PA | ETE |
| Water | | | | | | | | | | |
| *o-HBA* | 407 | *479* | 109 | 191 | *398* | 380 | *419* | 112 | 193 | *338* |
| *m-HBA* | *375* | 527 | *29* | 158 | *398* | *353* | 470 | 34 | 160 | 343 |
| *p-HBA* | *376* | 528 | 71 | *150* | 449 | *353* | 487 | *17* | *153* | 351 |
| Pentylethanoate | | | | | | | | | | |
| *o-HBA* | 430 | *437* | 258 | 444 | *251* | 394 | *399* | 246 | 429 | *217* |
| *m-HBA* | 357 | 518 | *104* | 355 | 267 | 336 | 478 | *110* | 350 | 237 |
| *p-HBA* | *350* | 485 | 130 | *343* | 272 | *326* | 431 | 147 | *338* | 240 |
| DMSO | | | | | | | | | | |
| *o-HBA* | 422 | *483* | 92 | 209 | *366* | 387 | *432* | 91 | 204 | *319* |
| *m-HBA* | 362 | 553 | *–37* | 136 | 379 | 340 | 482 | *–6* | 140 | 336 |
| *p-HBA* | *359* | 538 | –25 | *128* | 384 | *334* | 472 | –3 | *132* | 338 |
| Benzene | | | | | | | | | | |
| *o-HBA* | 440 | *424* | 425 | 694 | *155* | 401 | *398* | 392 | 658 | *132* |
| *m-HBA* | 353 | 516 | *247* | 589 | 173 | 332 | 432 | 289 | 565 | 157 |
| *p-HBA* | *342* | 462 | 288 | *572* | 179 | *317* | 420 | *287* | *547* | 160 |

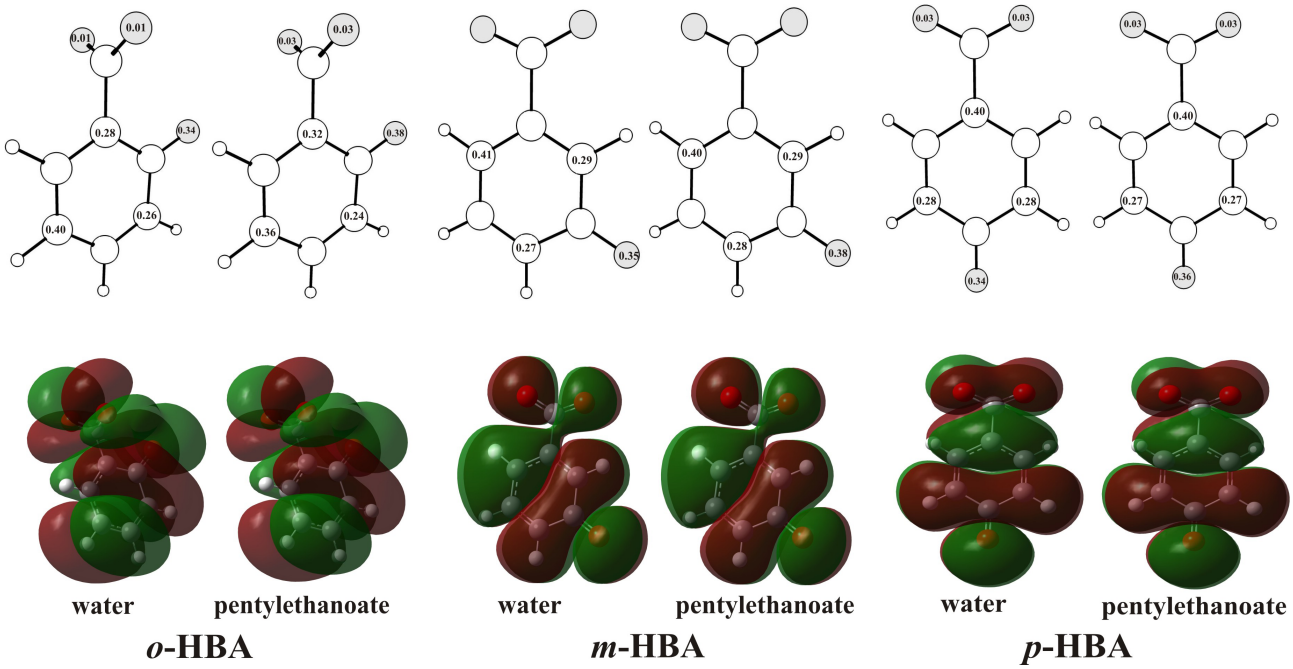


**Figure 3.** The spin density distribution (top) and SOMOs (bottom) of the phenoxyl radicals of carboxylate anions of hydroxybenzoic acids.

in both solvents. Analysis of spin density shows that *ortho* and *para* radicals are more stable than *meta* ones. Spin density on the carboxylate anion is also found in this case. The resonance radical structures play a very important role in their stabilization. *Ortho* and *para* radical forms have extended electron delocalization along the carboxylic anion.

### 2.3. Mechanism

It is well known that all monohydroxybenzoic acids have pK values between 3 and 4.5.[11] This means that at physiological pH of 7.4 all HBAs spontaneously hydrolyze, yielding the corresponding anions, namely the carboxyl group is almost entirely deprotonated, while at pH below 7 a significant portion of the molecules may be protonated. For these reasons, complete analysis of the mechanisms of antioxidative action should be investigated for both forms of HBAs. If Wright's rules, taking account of only HAT and SET-PT mechanisms, are ignored, the preferred antioxidative mechanism of HBAs and the corresponding anions can be predicted on the basis of BDE, IP, and PA values.[13,27–30] This means that the lowest of these three thermodynamic values could indicate which mechanism is more favorable under certain conditions.

#### 2.3.1. Mechanism of HBAs

On the basis of the thermodynamic data presented in Table 1 for neutral forms of HBAs, it is obvious that the HAT mechanism is dominant only in benzene, since BDE values of all HBAs are significantly lower in comparison to the corresponding IP and PA values. On the other hand, in other solvents, especially in the polar ones, PA values are significantly lower than BDE and IP values. This means that the SPLET mechanism is more probable than the other two. The data in Table 1 show that IP values are high for all HBAs in all solvents. This fact undoubtedly suggests that SET-PT is not a plausible mechanism under these conditions. The values of thermodynamic parameters, BDE and PA, show that the *p*-OH group is most reactive when radical scavenging takes place via the SPLET mechanism, while the *meta* position is more reactive in the case of the HAT mechanism. To confirm the obtained results, the DPPH and VCEAC experimental values are analyzed. DPPH values are expressed as Trolox equivalent antioxidant capacity (TEAC) values, while VCEAC values are defined as the antioxidant capacity equivalent to vitamin C concentration. The higher DPPH and VCEAC values for the compound under investigation indicate that the compound is a more efficient antioxidant. The obtained results are in agreement with experimental DPPH and VCEAC values predicting the *meta* position as slightly more reactive than the other two positions.[31,32] Moreover, the other theoretical results suggest competition between HAT and SPLET mechanisms in different solvents with various radicals.[12]

#### 2.3.2. Mechanism of HBAs' anions

The parameters of the antioxidant mechanisms for monoanions of HBAs in slightly alkaline water environment at physiological pH 7.4 are presented in Figure 2. As expected, SPLET is a more probable mechanistic pathway under these conditions. Moreover, thermodynamic values of the HBAs anions are calculated in the other three solvents. On the basis of the obtained results it is clear that the SPLET mechanism is a probable reaction pathway in DMSO, since PA values are significantly lower than the corresponding BDE and IP values.

On the basis of the mutual relationship between the PA and BDE values it is clear that the HAT mechanism is a predominant reaction path in benzene, while there is competition between the HAT and SPLET mechanisms in the other nonpolar solvent, pentylethanoate. The thermodynamic values of *o*-HBA are the exception in both solvents. Namely, IP and BDE values for the *o*-HBA anion in benzene are close, meaning

that SET-PT and HAT are competitive mechanisms in this medium. In pentylethanoate all three mechanisms are in competition since all three thermodynamic values are very close.

Although IP values of the anions are significantly lower than those for HBAs, they are still higher in comparison to BDEs and PAs in all media (except for *o*-HBA in benzene and pentylethanoate). This means that it is unlikely that the SET-PT is an operative mechanism under these conditions. The values of the thermodynamic parameters BDE, PA, and PDE (Table 2) indicate that the *p*-OH group should be a more reactive site in all solvents, meaning that the *p*-HBA anion is slightly better at radical scavenging than the other two.

Finally, it should be pointed out that theoretical predictions, based on the calculated thermodynamic properties of HBAs and the corresponding anions in various solvents, are in accordance with the known experimental data on the solvent effect on the free radical capability of phenolic compounds, and with DFT results on radical scavenging mechanisms based on the thermodynamic data.[12,25,27,28]

In this work, the phenolic OH bond dissociation enthalpies, ionization potential, and proton affinities related to HAT, SET-PT, and SPLET mechanisms of HBAs and corresponding anions were studied. For this purpose, the M05-2X/6-311++G(d,p) and B3LYP-D2/6-311++G(d,p) levels of theory were used. Although the BDE, IP, and PA values obtained by the B3LYP-D2 functional are generally smaller in comparison to M05-2X values, the same conclusions may be drawn using both levels of theory. The hydrogen atom from the 3-OH group of the *m*-HBA molecule proves to be more suitable for the abstractions in all solvents used. Therefore, this OH group obeys the HAT mechanism, which results in the formation of a stable HBA-3-O$^\bullet$ radical. On the other hand, the lowest PA values in all studied media are characteristic of the 4-OH group of *p*-HBA. This implies that, after the deprotonation as the first reaction step and electron transfer as the second reaction step, the 4-OH group yields a stable HBA-4-O$^\bullet$ radical. It is found that IP and PA values of HBAs and their anions significantly depend on the solvent polarity as a consequence of the additional stabilization of charged species by polar solvents (water and DMSO).

On the basis of the results obtained by both methods, the HAT mechanism proves to be dominant only in benzene. Since PAs of OH groups in polar solvents (water and DMSO) are significantly lower than corresponding BDEs, it is clear that the SPLET mechanism represents the dominant reaction pathway under these conditions. In pentylethanoate, as a nonpolar solvent, HAT and SPLET are competitive mechanisms in the case of monoanions of HBA, while SPLET is the most probable pathway when it comes to HBAs. Finally, it is important to emphasize that both HBAs and their anions in physiological conditions generally obey the SPLET antioxidant mechanism, while in the nonpolar solvents, which is comparable to the lipid environment, antioxidative action is mainly performed via the HAT mechanism. The obtained results showed that it is essential to perform calculations in different solvents, polar and nonpolar, to reveal the preferred mechanism of the antioxidative action of HBAs and corresponding monoanions.

## 3. Theoretical calculations

The equilibrium geometries of all hydroxybenzoic acids and corresponding radical cations, radicals, and anions were optimized by two different DFT methods, M05-2X and B3LYP-D2, and 6-311++G(d,p) basis set.[33,34] In this study all calculations were performed using Gaussian 09.[35] The M05-2X functional yields reasonable results for thermochemical calculations of organic, organometallic, and biological compounds, as well as for noncovalent interactions in investigated compounds.[36,37] This functional has also been successfully used by independent authors.[38–44] It is well known that this method satisfactorily reproduces experimentally determined

nonplanarity in the molecules such as fisetin, quercetin, and morin.[42,45] As is well known, Grimm's DFT-D can be successfully coupled with any DFT-based method. For the evaluation of investigated thermodynamic properties the B3LYP-D2 method was also used in this study.[46–48] B3LYP-D2 was selected as a widely applicable method that proved to describe interatomic interactions at short and medium distances ($\leq$5 Å) more accurately and reliably than traditional DFT methods. Hybrid GGA B3LYP-D2 includes an empirical correction term proposed by Grimme. The local and global minima were confirmed to be real minima by frequency analysis (no imaginary frequency were obtained). To evaluate the impact of different solvents, water, pentylethanoate, benzene, and DMSO were used. For this purpose, the SMD solvation model was used.[49] To mimic aqueous and lipid environments, water and pentylethanoate were used. The solvent effects are taken into account in all geometry optimizations and energy calculations by using the SMD model as implemented in Gaussian 09.[35,37] The NBO analysis of all species was carried out.[50,51]

BDE, IP, PDE, PA, and ETE values were determined from total enthalpies of the individual species as follows:

$$\mathrm{BDE} = H(\mathrm{HBA}-\mathrm{O}^{\bullet}) + H(\mathrm{H}^{\bullet}) - H(\mathrm{HBA}-\mathrm{OH}) \quad (6)$$

$$\mathrm{IP} = H(\mathrm{HBA}-\mathrm{OH}^{\bullet+}) + H(\mathrm{e}^{-}) - H(\mathrm{HBA}-\mathrm{OH}) \quad (7)$$

$$\mathrm{PDE} = H(\mathrm{HBA}-\mathrm{O}^{\bullet}) + H(\mathrm{H}^{+}) - H(\mathrm{HBA}-\mathrm{OH}^{\bullet+}) \quad (8)$$

$$\mathrm{PA} = H(\mathrm{HBA}-\mathrm{O}^{-}) + H(\mathrm{H}^{+}) - H(\mathrm{HBA}-\mathrm{OH}) \quad (9)$$

$$\mathrm{ETE} = H(\mathrm{HBA}-\mathrm{O}^{\bullet}) + H(\mathrm{e}^{-}) - H(\mathrm{HBA}-\mathrm{O}^{-}) \quad (10)$$

The values for solvation enthalpies of protons and electrons were taken from the literature.[52] Since the experimental essays for the determination of antioxidative activity are usually performed at room temperature, the temperature effects were not taken into account in simulations. Thus, all reaction enthalpies defined in Eqs. (6)–(10) were calculated at 298 K.

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