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Research Article

Free Radical Scavenging Potency of Dihydroxybenzoic Acids

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In order to evaluate the free radical scavenging potency of dihydroxybenzoic acids (DHBAs) the Density Functional Theory (DFT) was used. The M05-2X/6-311++G(d,p) and B3LYP-D2/6-311++G(d,p) theoretical models were applied. Three possible antioxidant mechanisms were examined: hydrogen atom transfer (HAT), single-electron transfer followed by proton transfer (SET-PT), and sequential proton loss electron transfer (SPLET) mechanisms. All of these mechanisms have been studied in nonpolar (benzene and pentylethanoate) and polar solvents (water) using an implicit solvation model (SMD). The following thermodynamic quantities related to these mechanisms were calculated: bond dissociation enthalpy (BDE), ionization potential (IP), and proton affinity (PA). The obtained results indicated the HAT mechanism as the most favourable reaction pathway for antioxidative action of DHBAs in benzene. On the other hand, SPLET is indicated as predominant reaction mechanism in polar solvent. The SET-PT mechanism was not favourable reaction path for antioxidative action in any of the solvents under investigation.

1. Introduction

Oxidative stress plays an important role in the pathogenesis of many diseases [1–5]. To neutralize the damaging effect of free radicals, the organisms often use some external factors including the dietary substances, such as phenolics, which can help in prevention of free radical damage. These substances constitute complex antioxidant defence systems. Phenolic acids are the group of the naturally occurring compounds which, besides one carboxylic acid functionality, have the common structural features as all phenolics: an aromatic ring bearing one or more hydroxyl substituents. There are two types of the phenolic acids: hydroxycinnamic (HCA) and hydroxybenzoic acids (HBA) [6, 7]. They are constituents of almost all vegetables, fruits, and grains. They can be found in the free state, but most commonly they are occurring in plant materials linked through esters, ethers, or as structural components of the cellulose, proteins, and lignins [8–10]. There is some evidence affirming multiple roles and functions of the phenolic acids and indicating these compounds as involved in processes such as the protein synthesis, nutrient uptake, enzyme activity, photosynthesis, and allelopathy [11–13]. There are also a number of the epidemiological investigations [14–17] which confirm a possible connection between the consumption of food containing phenolics and the reduced risk of developing some disorders, including cancer and cardiovascular diseases. However their in vivo role is still unknown.

It has been proposed that the antioxidant activity of HBA depends on the number of hydroxyl groups in a molecule [18] and that it increases following the order: monohydroxy, dihydroxy, and trihydroxy, respectively [19]. Dihydroxybenzoic acids (DHBA) are a subclass of hydroxybenzoic acids possessing two hydroxyl groups whose relative position determines the properties of molecules. There are some experimental evidences which generally confirm good antioxidant activity of DHBAs [20, 21], especially indicating good scavenging potency of 3,4-DHBA and 2,3-DHBA. Protocatechuic acid (3,4-DHBA) is a strong antiradical and antioxidant agent which inhibits the chemical carcinogenesis and show protection against the hydroperoxide-induced toxicity [22]. Also, a few positive health attributes of 3,4-DHBA such as antibacterial [23], antimutagenic [24], anti-inflammatory, anticoagulatory [25], and antihyperglycemic [26] actions have been reported. Although all these compounds can be found in natural products there are certain findings which implicate the nonenzymatic production of 2,3-DHBA (pyrocatehuic acid), which proceeds upon trapping the hydroxyl radical by salicylic acid [27]. Moreover, pyrocatehuic acid may act as a metabolite of dioxygenases [28].

As mentioned, the antioxidant ability of the phenolic acids is greatly influenced by the number and the relative position of the hydroxyl groups in the ring. It has been also suggested that the proximity of the hydroxyl groups to the acid moiety promotes the hydrogen atom transfer from the phenolic acid (PhO-H) to the radical specie. In the radical scavenging mechanisms the reactive radical specie is inactivated by accepting a hydrogen atom from a hydroxyl group of the phenolic acid. Phenolic acids can scavenge free radicals through three competitive mechanisms, which are generally influenced by the reaction conditions. The suggested mechanisms are hydrogen atom transfer (HAT, (1)), single-electron transfer followed by proton transfer (SET-PT, (2a) and (2b)), and sequential proton loss electron transfer (SPLET, (3a) and (3b)) [29–36]:

$$\text{Ph-OH} \longrightarrow \text{Ph-O}^{\bullet} + \text{H}^{\bullet} \quad (1)$$

$$\text{Ph-OH} \longrightarrow \text{PhOH}^{+\bullet} + \text{e}^{-} \quad (2a)$$

$$\text{Ph-OH}^{+\bullet} \longrightarrow \text{Ph-O}^{\bullet} + \text{H}^{+} \quad (2b)$$

$$\text{Ph-OH} \longrightarrow \text{Ph-O}^{-} + \text{H}^{+} \quad (3a)$$

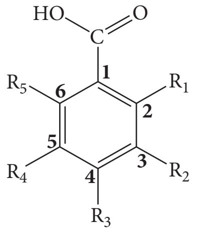
$$\text{Ph-O}^{-} \longrightarrow \text{Ph-O}^{\bullet} + \text{e}^{-} \quad (3b)$$

From the presented equations, it is clear that all these mechanisms have the same net result: formation of the corresponding phenoxyl radical which is more stable and less reactive than the free radical specie. The antioxidative mechanisms mentioned above are characterized with the thermodynamic parameters: bond dissociation enthalpy (BDE) related to (1), ionization potential (IP) related to (2a), proton dissociation enthalpy (PDE) related to (2b), proton affinity (PA) related to (3a), and electron transfer enthalpy (ETE) related to (3b).

In this paper, we aimed to provide thermodynamical parameters, related to the antiradical mechanism, that can implicate the antioxidant activity of six DHBAs: 2,3-dihydroxybenzoic acid (2-pyrocatechuic acid or hypogallic acid); 2,4-dihydroxybenzoic acid (β-resorcylic acid); 2,5-dihydroxybenzoic acid (gentisic acid); 2,6-dihydroxybenzoic acid (gamma-resorcylic acid or 2,6-resorcylic acid); 3,4dihydroxybenzoic acid (protocatechuic acid), and 3,5-dihydroxybenzoic acid (α-resorcylic acid) (Figure 1).

2. Methodology Section

All calculations were performed using Gaussian 09 program package [37], and two levels of theory were applied. The optimized geometries of the investigated dihydroxybenzoic acids and the corresponding radicals, anions, and radical cations were obtained by M05-2X method, in combination with 6-311++G(d,p) basis set [38, 39]. This hybrid functional, initially developed by Truhlar group [38], gives satisfactory results in the thermochemical and kinetic calculations and has been used widely by numerous authors [40–44].



R_1=R_2=R_3=R_4=R_5=OH

(**1**) R_1, R_2	(**4**) R_1, R_5
(**2**) R_1, R_3	(**5**) R_2, R_3
(**3**) R_1, R_4	(**6**) R_2, R_4

Figure 1: Structural formulas of the examined dihydroxybenzoic acids (**1**, **2**, **3**, **4**, **5**, and **6**) with atom labeling indicated and their trivial names.

The other applied method is B3LYP-D2, developed by Grimme [45, 46]. This functional can be efficiently coupled with any existing DFT method. It is proved that this method describes the interatomic interactions at short and medium distances (≤5 Å) reliably and more accurately than the traditional DFT methods. For including a long-range dispersion contributions to the computed DFT total energy and gradients at the B3LYP level of theory [47, 48], Grimme [46] and Bayach et al. [49] used an atom-atom additive damped empirical potential of the form $-f(R)C_6/R^6$:

$$E_{\text{B3LYP-D2}} = E_{\text{B3LYP}} - E_{\text{Disp}}, \quad (4)$$

where C_6 is the dispersion coefficient for the pair of atoms, R is the interatomic distance between atoms, and E_{Disp} is the empirical term. Both M05-2X and B3LYP-D2 methods were chosen, primarily because of being widely used and secondly because these methods describe very well the interatomic interactions at short and medium distances. These methods are more reliable and accurate than traditional density function methods.

Potential energy minima for all the optimized species are verified by the absence of the imaginary frequencies. Influence of water, pentylethanoate, and benzene was estimated using SMD solvation model [50]. The SMD continuum model allows the quantum mechanical approach in studying the interactions of the solvated molecules. The selected solvents enable investigating the behaviour of the molecules in polar and nonpolar environment. The delocalization effects were assessed within the NBO analysis framework [51].

The thermodynamical parameters relevant for the investigated antioxidative mechanisms (BDE, IP, PDE, PA, and ETE) were calculated from total enthalpies of the optimized species using the following equations:

$$\text{BDE} = H\left(\text{Ph-O}^{\bullet}\right) + H\left(\text{H}^{\bullet}\right) - H\left(\text{Ph-OH}\right) \quad (5)$$

$$\text{IP} = H\left(\text{Ph-OH}^{\bullet+}\right) + H\left(\text{e}^{-}\right) - H\left(\text{Ph-OH}\right) \quad (6a)$$

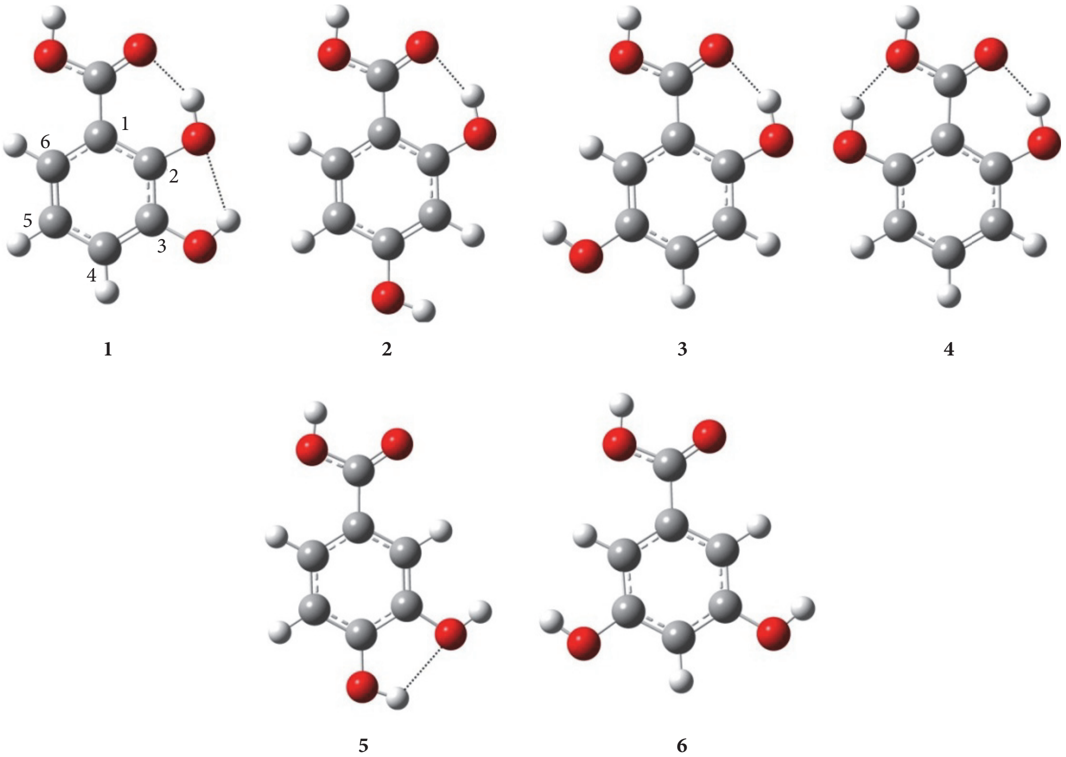


Figure 2: The most stable structures of the examined DHBAs.

$$\text{PDE} = H\left(\text{Ph-O}^{\bullet}\right) + H\left(\text{H}^{+}\right) - H\left(\text{Ph-OH}^{\bullet+}\right) \quad (6b)$$

$$\text{PA} = H\left(\text{Ph-O}^{-}\right) + H\left(\text{H}^{+}\right) - H\left(\text{Ph-OH}\right) \quad (7a)$$

$$\text{ETE} = H\left(\text{Ph-O}^{\bullet}\right) + H\left(\text{e}^{-}\right) - H\left(\text{Ph-O}^{-}\right) \quad (7b)$$

The recommended values of the solvation enthalpies of the protons and electrons were taken from the literature [52]. The reaction enthalpies were calculated at 298.15 K, with the temperature effects not taken into the account.

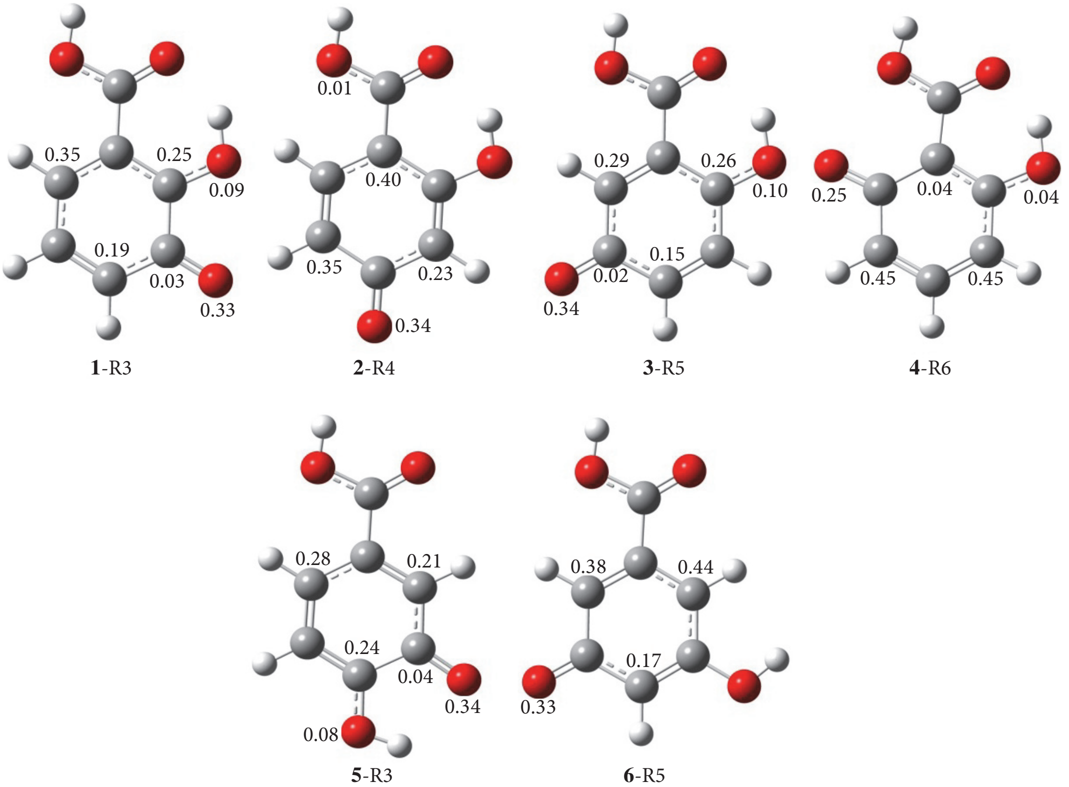
3. Results and Discussion

The conformational analysis of DHBAs was carried out. For this purpose, different conformations were obtained in the following way. First, two structures of each DHBA were constructed by placing the carboxyl group into two extreme positions (rotation around the C-C bond by 180°). Then, each of these structures was analysed by different orientations of hydrogen atom (antiperiplanar and synperiplanar) of different hydroxyl groups. All the rotamers of DHBAs are presented in Supplementary Material available online at https://doi.org/10.1155/2017/5936239 (Figures S1–S6). The tables shown in Supplementary Material (Tables S1–S6) indicate the energy differences between the investigated rotamers of all the compounds under investigation. The most stable structures are presented in Figure 2.

The structures of the all DHBAs presented in Figure 2 are planar and have at least one internal hydrogen bond (IHB). Namely, compounds which possess the hydroxyl group in position C2 have IHB between hydrogen atom of the hydroxyl group and carbonyl oxygen of the carboxyl group. Compounds **1** and **4** form one more IHB that contribute to the stability of these molecules. The oxygen atoms of the carbonyl and hydroxyl groups possess the lone electrons located in the antibonding orbitals. These lone pair-antibonding orbital interactions, between the oxygen and the adjacent O-H bonds, are responsible, as revealed by the NBO analysis, for IHB formation. The energy values presented in Tables S1–S6 confirm that the most stable rotamers are those with the highest number of IHBs, especially the ones that include IHBs with carbonyl oxygen. Also it is evident from Figure 2 that compounds **4** and **6** are symmetrical molecules. In further discussion only the species generated from the most stable rotamers will be discussed.

3.1. Radicals and Anions of DHBAs. Investigation of the antioxidant activity of DHBs was conducted to the OH groups. This restriction to the OH groups is supported by the fact that the protons of hydroxyl groups are more acidic than the proton of carboxylic group [53, 54]. The homolytic breaking of the O-H bonds in DHBAs results in formation of the radicals (Figure 3). The stability of the formed radicals, in water, plays the main role in determining the antioxidant activity of the investigated molecules. The obtained values of BDE are given in Tables 1 and 2.

The stability of the formed radicals in water is decreasing in the following order: **3** > **5** > **1** > **4** > **6** > **2**, while the order in pentylethanoate and benzene is **5** > **3** > **1** > **6** > **4** > **2**. This result implies the homolytic cleavage of the 5-OH bond, in the polar solvent, as the favoured one in compound **3**,



1-R3 **2**-R4 **3**-R5 **4**-R6

5-R3 **6**-R5

Figure 3: Spin density distribution in all DHBA's radicals in water.

meaning that the **3**-R5 radical is the most stable radical of the investigated compounds. On the other hand, the homolytic cleavage of the 3-OH bond, in nonpolar solvents, is the favoured one in compound **5** (**5**-R3).

In order to rationalise the differences in BDE and consequently the differences in the reactivity of the individual OH sites the assessment of the spin density distribution was undertaken on the DHBA's radicals. The lower BDE values implicate easier formation of the radicals and more delocalized spin density [55]. The spin density values in water, obtained by the NBO analysis, as well as SOMOs of DHBAs are depicted in Figures 3 and S7. The results show that the radicals formed from compounds **3**, **5**, and **1** are the most stable. This is consequence of delocalization of their unpaired electrons over oxygen and carbons (O5, C2, C4, and C6 in **3**-R5; O3, C2, C4, and C6 in **5**-R3; and O3, C2, C4, and C6 in **1**-R3). The unpaired electron of **5**-R3 can be additionally delocalized only over the one adjacent OH group, 4-OH (Figure 3). Also, the unpaired electrons are well delocalized in radicals obtained by the homolytic cleavage of the O-H bond in other compounds (**2**, **4**, and **6**).

The heterolytic cleavage of the O-H bond results in forming the corresponding anions. The obtained PA values of all OH groups (in compounds **1**–**6**), as well as in all solvents under investigation, presented in Tables 1 and 2, follow the sequence **5**-A4 > **2**-A4 > **1**-A2 > **4**-A6 > **6**-A5 > **3**-A5. This result implicates the proton transfer from the 4-OH group of the compound **5** as easier than the transfer from the other OH groups. It should be noted that the obtained PA values are significantly lower in water (polar solvent) than the other two, nonpolar, solvents (benzene and pentylethanoate). The reason for this is change of the solvent polarity, which influences the increase of PA values as the solvent polarity increases. This is a consequence of the higher solvation enthalpy of protons.

The natural charge distributions of all anions, formed by heterolytic cleavage of O-H bonds of the DHBAs, are presented in Figure 4. Two, the most stable, anions are obtained by deprotonation of the O-H bonds of the *para* phenolic groups of compounds **2** and **5**. The negative charges, which contribute to the stability of these anions, are delocalized over O4, C1, C3, C5, and C6 atoms in **2**-A4 and over O4, C1, C2, C5, and C6 atoms in **5**-A4. The deprotonated oxygen atom in **5**-A4 forms, with the neighbouring 3OH group, one hydrogen bond, which causes lower PA value and additionally contributes to the stability of this anion.

3.2. Free Radical Scavenging Mechanisms. As mentioned above, three mechanisms of free radical scavenging activity of DHBAs (HAT, SET-PT, and SPLET) were the subject of this study. Reaction enthalpies related to these mechanisms are calculated using (5)–(7b) and by applying two DFT methods. The values of BDE, PA, and IP are used for the estimation of the preferred mechanisms of the antiradical activity of the investigated DHBAs [56–58]. The species needed to complete the thermodynamic calculations are generated from the most stable conformation of the investigated compounds.

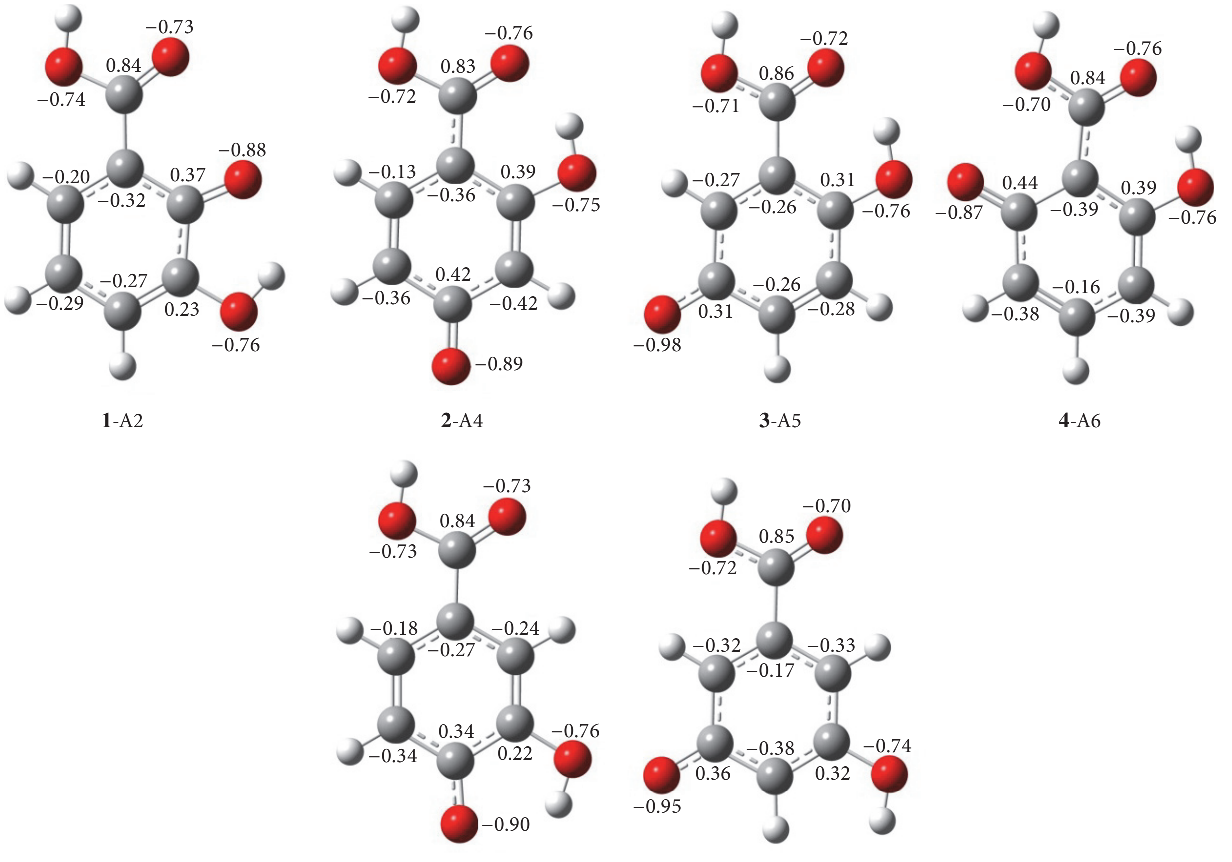
If the calculated values obtained by both theoretical methods (Tables 1 and 2) are compared, it is clear that the thermodynamic parameters calculated using the B3LYP-D2

Table 1: M052X/6-311++G(d,p) calculated parameters of the antioxidant mechanisms for DHBAs in kJ mol^{-1} in all solvents under investigation.

Compounds	Water					Benzene					Pentylethanoate				
	HAT	SET-PT		SPLET		HAT	SET-PT		SPLET		HAT	SET-PT		SPLET	
	BDE	IP	PDE	PA	ETE	BDE	IP	PDE	PA	ETE	BDE	IP	PDE	PA	ETE
1		518					673					592			
2-OH	369		32	132	419	377		120	423	370	374		46	262	376
3-OH	362		25	145	405	366		109	434	356	371		35	273	341
2		550					703					622			
2-OH	408		39	146	442	420		133	452	384	415		58	290	390
4-OH	401		31	129	452	392		105	401	406	392		35	244	412
3		504					658					577			
2-OH	373		49	153	400	389		147	461	343	383		71	298	349
5-OH	358		34	153	386	350		108	444	321	350		38	284	331
4		521					674					593			
2-OH	391		51	149	423	403		145	448	371	399		70	286	378
6-OH	380		39	137	423	381		123	423	374	379		51	264	380
5		532					693					611			
3-OH	361		9	130	411	346		69	401	361	347		1	244	368
4-OH	364		12	119	425	347		70	383	380	349		3	227	386
6		537					697					613			
3-OH	383		27	144	419	375		93	429	362	374		26	269	371
5-OH	382		26	143	419	374		92	427	362	374		25	268	371

Table 2: B3LYP-D2/6-311++G(d,p) calculated parameters of the antioxidant mechanisms for DHBAs in kJ mol^{-1} in all solvents under investigation.

Compounds	Water					Benzene					Pentylethanoate				
	HAT	SET-PT		SPLET		HAT	SET-PT		SPLET		HAT	SET-PT		SPLET	
	BDE	IP	PDE	PA	ETE	BDE	IP	PDE	PA	ETE	BDE	IP	PDE	PA	ETE
1		462					643					559			
2-OH	348		37	135	364	356		102	401	344	352		44	257	346
3-OH	341		30	147	345	345		91	426	309	341		34	278	314
2		492					670					586			
2-OH	386		45	151	386	397		116	431	355	392		58	286	358
4-OH	376		35	131	396	367		87	380	377	367		33	239	379
3		448					627					542			
2-OH	352		56	157	346	367		130	438	319	362		71	293	320
5-OH	337		40	155	333	330		92	420	299	329		39	276	304
4		461					646					562			
2-OH	367		56	148	370	382		126	427	345	378		68	281	348
6-OH	356		46	137	370	363		106	405	348	360		50	261	350
5		474					660					575			
3-OH	339		16	132	358	325		54	378	337	325		2	237	340
4-OH	341		18	120	371	325		54	359	355	326		3	221	357
6		480					665					577			
3-OH	361		32	147	365	353		79	407	336	353		27	263	341
5-OH	360		31	146	365	352		77	406	336	352		26	263	341



1-A2 **2**-A4 **3**-A5 **4**-A6

5-A4 **6**-A5

Figure 4: The natural charge distributions in the most stable anions formed from the investigated DHBAs in water.

functional are mainly lower. Having that in mind, the further discussion will refer to both used methods.

From Tables 1 and 2, it is clear that the IP values for all DHBAs calculated at both theoretical levels, as well as in all solvents investigated, are highly implicating SET-PT as nonoperative mechanism. On the other hand, looking at the obtained results, it is evident that in water and pentylethanoate the PA values are significantly lower than the corresponding BDE values. However, it should be pointed out that PA values are much higher in pentylethanoate than in water which indicates the SPLET mechanism as the most probable reaction pathway in those solvents. Taking into the account BDE and PA values in benzene as classical nonpolar solvent it is evident that BDE values are significantly lower than the corresponding PA values, which proves that the reaction in benzene proceeds via HAT mechanism. Further analysis of the thermodynamic values (Tables 1 and 2) indicates that compounds **5** and **1** have the best antioxidant activity in all solvents under investigation.

The BDE values obtained for the investigated DHBAs are lower than those for phenol (406.4 and 382.8 kJ mol^{-1}), resveratrol (368.8 and 356.2 kJ mol^{-1}), and caffeic acid (359.9 and 342.52 kJ mol^{-1}) [59], obtained with B3LYP method in water and benzene, as solvents. Comparing examined dihydroxybenzoic acids with the other phenolic acids, such as hydroxybenzoic acids and gallic acid [40, 41], it is clear that dihydroxybenzoic acids show quite good antioxidative properties. Among all the mentioned acids gallic acid shows the best antioxidant activity proving the significance of the number of hydroxyl groups in such activity [41]. Our results are in good accordance with previous results [40, 41, 60].

4. Conclusions

The generally accepted approach based on the thermodynamic parameters (BDE, IP, and PA), related to the HAT, SPLET, and SET-PT mechanisms, was applied to six dihydroxybenzoic acids, their radicals, and the corresponding radical cations and anions. Calculated energy requirements indicate thermodynamically plausible radical scavenging mechanisms. The calculations performed with two theoretical models, B3LYP-D2 and M05-2X, in polar and nonpolar solvents, proved to be in good accordance.

The obtained results indicate HAT as thermodynamically favourable mechanism in benzene and SPLET in water and pentylethanoate. Calculated energy requirements indicated that compounds **5** and **1** have better radical scavenging properties than other DHBAs.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

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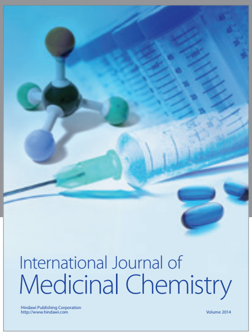

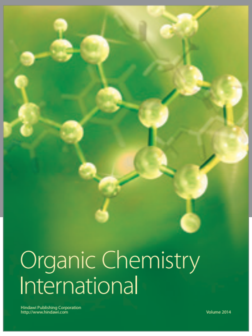

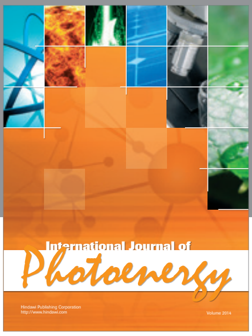

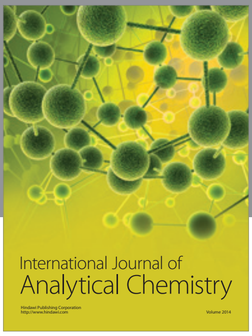

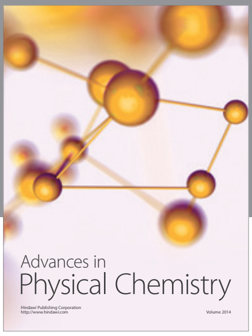

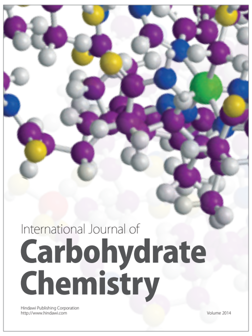

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