A Computational Study of the Structure–Activity Relationships of Some *p*-Hydroxybenzoic Acid Antioxidants

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ABSTRACT: Equilibrium structures of all derivatized systems of *p*-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, 3-methoxy-4-hydroxybenzoic acid, and 3,5-dimethoxy-4-hydroxybenzoic acid and calculated structural and energetic molecular descriptors were determined at the B3LYP/6-31+G(d) density functional theoretical level in an attempt to study their structure–activity relationships (SAR). The theoretical antioxidant activity trend, derived in terms of hydrogen-donating capacity against radicals in lipid systems, is in excellent agreement with the experimental one. The lower antioxidant activity of benzoates, experimentally found relative to the homologous cinnamates, could be due to (i) their lower spin delocalization, (ii) their higher calculated heats of formation values in forming radicals (ΔHOF), and (iii) the much stronger electron-withdrawing effect of the –COOH group than –CH=CHCOOH. The low calculated dipole moment values of the global minimum structures of the antioxidants could facilitate their solubilities in nonpolar solvents, hence the ease of hydrogen abstraction. However, highest occupied molecular orbital (HOMO) eigenvalues can neither predict antioxidant activity nor differentiate the same activity between two series of structurally related compounds. Again, density functional theory calculations provide a good molecular descriptor, ΔHOF, to correlate with the antioxidant activity in molecules showing similar structural characteristics.

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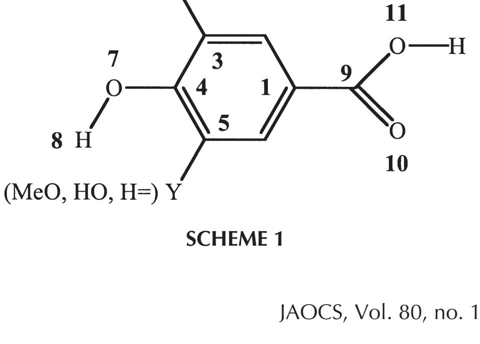
KEY WORDS: Antioxidant, B3LYP, BDE, DFT, 3,4-dihydroxybenzoic acid, ΔHOF, *p*-hydroxybenzoic acid, 4-hydroxy-3,5-dimethoxybenzoic acid, 4-hydroxy-5-methoxybenzoic acid, structure–activity relationships.

As part of a continuing investigation of the structure–activity relationships (SAR) of phenolic antioxidants (1–3), we have embarked on a project to investigate their structures and energetics in the gas phase. This investigation was based on structural factors because the nature of the phenyl-ring substituents and the presence and position of a double bond in the side chain lead to minor structural differences for the compounds under study. The density functional theory/Becke's three parameter hybrid functional using the Lee–Yang–Parr correlation functional theory (DFT/B3LYP)-calculated value for heat of formation value of the phenoxyl radical, ΔHOF (also denoted as bond dissociation enthalpy, BDE), appears as a meaningful molecular descriptor of antioxidant activity in accordance with experimental data. The degree of conjugation and the calculated spin delocalization values in the phenoxyl radicals also could explain the scavenging activity. Moreover, ΔHOF differences derived between antioxidants exhibiting either extended or minor molecular conjugations are small (2,3). However, the presence of one double bond in the side chain makes a difference in the antioxidant activity if it leads to an extended conjugation. The role of the catechol moiety in the antiradical efficacy of the *p*-hydroxycinnamic acid derivatives also was theoretically proven (1).

p-Hydroxybenzoic acid antioxidants, with the general structure shown in Scheme 1, have not been subjected to systematic and rigorous theoretical investigation. They present a shorter (by one ethylenic group) side chain than *p*-hydroxycinnamic acid derivatives (thereafter denoted as cinnamates), their structural analogs. Hence, they constitute an excellent series of compounds for studying the influence on antioxidant activity of the presence of one double bond in the side chain. Moreover, this particular bond could differentiate between the electronic effects of the side-chain substituents in benzoates and cinnamates. For comparison, only the *p*-hydroxybenzoic acid homolog derivatives of cinnamates are studied herein, at the same theoretical level.

The present study deals with the structures and stereochemical features of all possible derivatized systems of the *p*-hydroxybenzoic acid antioxidants, namely, **I**, *p*-hydroxybenzoic acid; **II**, 3,4-dihydroxybenzoic acid (protocatechuic acid); **III**, 3-methoxy-4-hydroxybenzoic acid (vanillic acid); and **IV**, 3,5-dimethoxy-4-hydroxybenzoic acid (syringic acid). The following considerations emphasize their novel aspects.

Since **I** contains two different conjugating substituents at the 1,4-positions (the carboxyl and hydroxyl groups), planar derivatized systems arise, which may be labeled *E* and *Z*. The



SCHEME 1

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presence of two hydroxyl groups in **II** leads to a larger number of *E* or *Z* planar forms. Nonplanar forms also may arise from the methoxy groups in **III** and **IV**. The rotation of the COOH group around the C–COOH single bond by 180° affords additional *Z* and *E* forms in **II**, **III**, and **IV**. In contrast to **I**, which exhibits a single corresponding radical form, **II**, **III**, and **IV** have four or more. Hence, the possible number of respective parent–radical pairs increases in the latter antioxidants compared to **I**.

To our knowledge, theoretical energetics and structural data for the molecules under examination have not been previously reported. Tyrakowska *et al.* (4) studied the experimental [Trolox equivalent antioxidant capacity (TEAC) assay] and theoretical antioxidant activities of some 4-hydroxybenzoates (vanillic acid was not included) at the B3LYP/6-311+G(d,p) theoretical level to determine how their antioxidant behaviors are affected by the numbers and positions of OH groups. They determined the ΔHF values between the mono-anionic and the di-anionic forms of the parent compounds. In contrast, our study focuses on the values corresponding to the homolytic dissociation of the phenolic OH group of a neutral parent compound. In addition, we report on structural and frequency data. X-ray crystallographic data are available for only one [*p*-hydroxybenzoic acid (5,6)] of the four acids under study.

Calculations resulted in (i) optimization of the geometries of the antioxidants and their respective phenoxyl radicals, (ii) determination of their vibrational frequencies, and (iii) evaluation of the corresponding ΔHOF values, spin density values, and highest occupied molecular orbital (HOMO) eigenvalues.

THEORETICAL METHODS

Details on the calculation of the ΔHOF values and on the geometries of all minimum-energy structures for the parent molecules—which were fully optimized by using DFT calculations (7) and the B3LYP functional (UB3LYP for the resulting radicals) with the 6-31+G(d) basis set—were given in previous papers (1,3). All calculations were carried out using the GAUSSIAN 98 program suite (8).

Rotation energy profiles around the C_{phenyl}–$O_{hydroxyl}$ and C_{phenyl}–$C_{carboxyl}$ bonds were determined at $\theta = 15°$ intervals of the dihedral angle between the planes of the benzene ring and the C–OH or the carboxyl COOH plane. In both cases full structural optimizations were performed, which decreased the barrier height by 0.7 and 0.3 kcal/mol, respectively, compared to those calculated by nonstructural optimization. When performing full geometry optimizations, the dihedral angle between the planes of the benzene ring and the C–OH or the carbonyl COOH planes was set at a constant value, whereas all other parameters were allowed to optimize.

RESULTS AND DISCUSSION

A complete knowledge of the geometries of the antioxidants and their respective phenoxyl radicals is a prerequisite for studying their SAR. Since only the structure of *p*-hydroxybenzoic acid has been investigated (5,6,9), all local and global structural minima on the potential energy hypersurface of the parent antioxidants and their phenoxyl radicals have been fully identified.

Equilibrium geometries. Global-minimum structures of the four parent compounds, **I**–**IV**, together with selected geometric data, are shown in Figure 1. In the following discussion as well as in Figure 1 and Table SI and Figure S1 (the latter two available upon request from the author; *vide infra*), *E* and/or *Z* forms denote the orientation of the H atom of the *para*-OH group, relative to the carbonyl oxygen of the carboxyl functional group. *Syn* and *anti* differentiate the orientation of the OH and/or Me groups at the *meta*-positions, relative to the H atom of the *para*-OH group. Square brackets denote the out-of-the molecular plane Me groups. The equilibrium structures and dipole moment values of all of the parent molecule conformers are given as Supplementary Material (Fig. S1). We discuss the compounds individually prior to drawing conclusions of a more general nature.

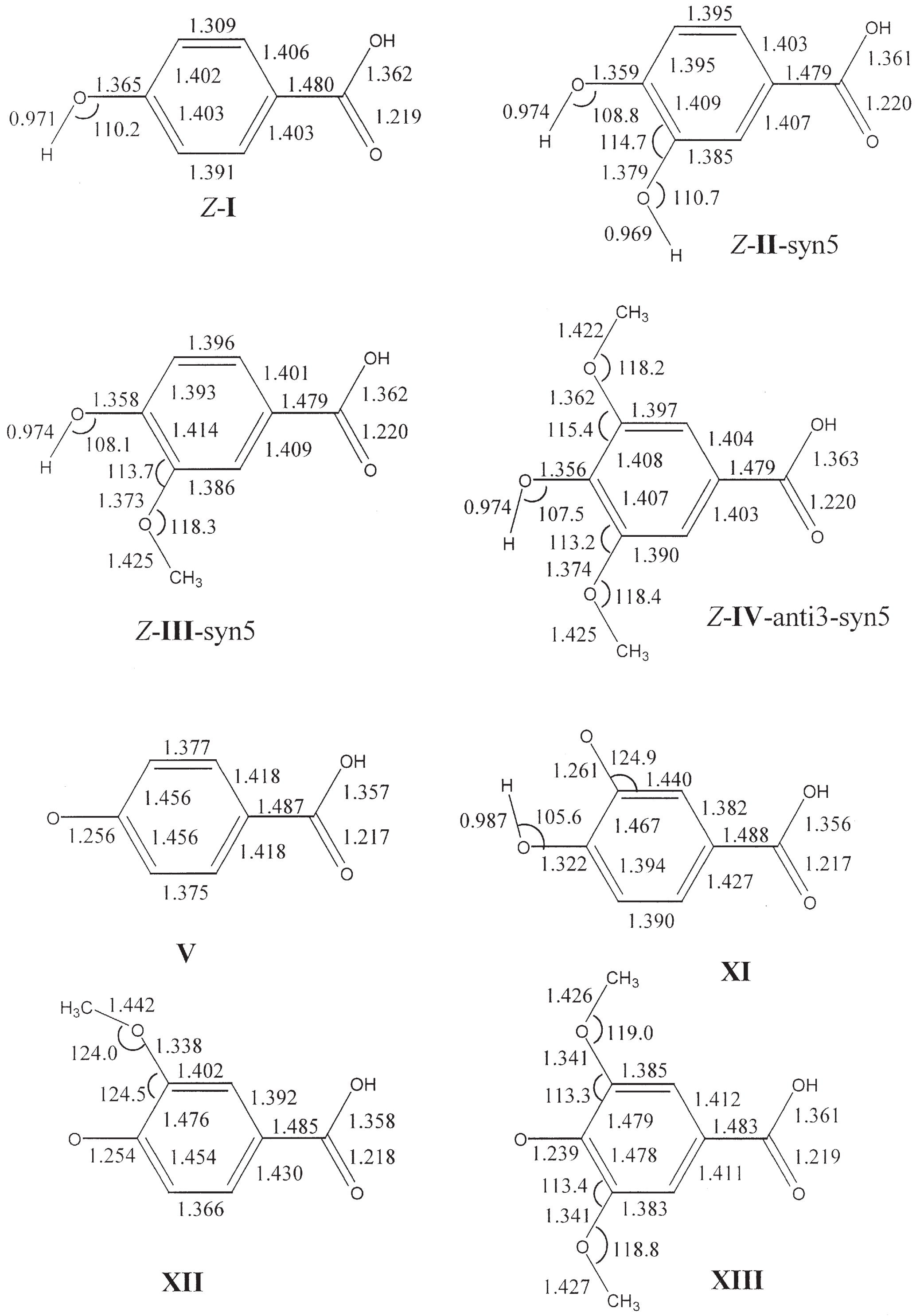
p-*Hydroxybenzoic acid (**I**)*. The monohydrate (5) and the dimeric form (6) of this compound have been characterized experimentally and studied theoretically (9) and serve as a reference for the structural and energetic changes predicted for the derivatized systems.

Both predicted *Z*-**I** and *E*-**I** (not shown in Fig. 1) equilibrium geometries of **I** are planar, in close agreement with existing experimental and theoretical data. Unlike the experimental data (5), the former conformation is energetically favored over the latter by 0.06 kcal/mol. Wiberg (10) calculated an energy difference between the *Z* and *E* conformers of less than 0.1 kcal/mol and found that the proton of an electron-releasing substituent such as OH in the *para*-position of the benzoic acid prefers to be on the C=O side of the COOH group, in excellent agreement with our theoretical results. Selected structural parameters at the calculated optimized geometries for **I** are given in Table SI, along with the available corresponding X-ray and theoretical structural data. An inspection of the numbers appearing in the table clearly shows that (i) the corresponding computed structural parameters are in agreement within 0.5% or better and, (ii) with few exceptions, agreement with the available experimental ones is within 1% or better.

The potential energy profiles for the rotation of OH and COOH groups of **I** are investigated next and are shown in Figure 2. The rotational transition structures of the two bonds in **I** were fully optimized using the saddle points in the potential energy surface as initial structures.

Rotation of the OH and COOH groups gave the energy maximum at 92 and 89º [dihedral angle values of C(3)–C(4)–O(7)–H(8) and C(2)–C(1)–C(9)–O(10) in the corresponding transition states, respectively] with barriers of 3.75 and 7.50 kcal/mol, respectively. As expected (11), the rotational barrier of the same groups, calculated by the Austin model 1 (AM1) method, was about 50% lower (2.31 and 2.69 kcal/mol, respectively) than the DFT results. The former value is in fairly good agreement with that derived at the MP2/6-311++G** (2.60 kcal/mol) (10). Moreover, the available theoretical value (5.90 kcal/mol) for the C_{phenyl}–$C_{carboxyl}$ rotation in *p*-OH-ethylbenzoate (12) is in better agreement with our calculated value of

7.5 kcal/mol. Figure 2 shows that, in the case of the C_{phenyl}–$C_{carboxyl}$ rotation, the energy minima occur at $\theta = 0$, 180, and 360° (not shown in Fig. 2), corresponding to the planar conformations, and these are stabilized by resonance structures, permitting the conjugated π-electron system to delocalize so as to include the carbonyl group. When the C_{phenyl}–$C_{carboxyl}$ bond is rotated 90°, resonance stabilization is eliminated and there is an increase in energy. It is interesting to note that the energy



Z-**I**

Z-**II**-syn5

Z-**III**-syn5

Z-**IV**-anti3-syn5

V

XI

XII

XIII

FIG. 1. Global-minimum geometries of the parent molecules and their respective radicals, optimized at the B3LYP/6-31+G(d) level. Bond lengths are in angstroms and angles in degrees. (For an explanation of the symbols see text).

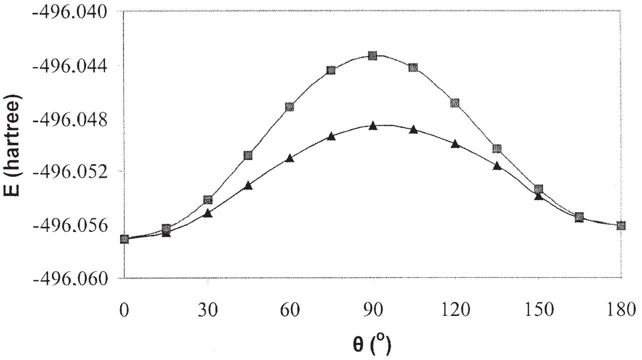


FIG. 2. Potential energy profiles for the rotation of OH (▲) and COOH (■) groups of **I** *p*-hydroxybenzoic acid.

minimum at θ = 0° (*Z*-**I**) is transformed to the *E*-**I** one upon 180° C_{phenyl}–$C_{carboxyl}$ rotation; a further rotation of 180° again yields the *Z*-**I**. On the other hand, *Z*-**I** is transformed to *E*-**I** by a simple 180° C_{phenyl}–$O_{hydroxyl}$ rotation.

*(ii) 3,4-Dihydroxybenzoic acid (**II**).* A set of six planar structures is associated with **II**. The global-minimum structure derived, *Z*-**II**-*syn*5 form (*toward* conformer), is more stable than the *E*-**II**-*anti*5 and *E*-**II**-*syn*5 ones (*away* conformers) by 1.10 and 4.34 kcal/mol, respectively. Moreover, it is more stable by 0.35, 0.96, and 4.58 kcal/mol than the *E*-**II**-*anti*3, *Z*-**II**-*syn*3, and *Z*-**II**-*anti*3 ones, respectively, derived by 180° rotation around the C–COOH single bond. The global-minimum structure derived is also in close agreement with the substituent effect study of Reference 10, which predicted that electron-releasing substituents, such as OH, in the *meta*-position of the *p*-hydroxybenzoic acid prefer to be on the C=O side of the COOH group.

*(iii) 3-Methoxy-4-hydroxybenzoic acid (**III**).* There are six local minima on the potential energy hypersurface of **III**. Unlike **I** and **II**, **III** has also nonplanar forms, i.e., the *E*-**III**-[*anti*5] and *Z*-**III**-[*syn*3] ones, in which the Me groups are out of the molecular plane by 69.6 and 69.1°, respectively. In **III**, the *E*-**III**-*syn*5, *E*-**III**-[*anti*5], *E*-**III**-*anti*3, *Z*-**III**-*anti*3, and *Z*-**III**-[*syn*3] forms are 4.70, 6.53, 0.37, 4.94, and 6.41 kcal/mol, respectively, above the global-minimum energy conformer, *Z*-**III**-*syn*5.

*(iv) 3,5-Dimethoxy-4-hydroxybenzoic acid (**IV**).* Four stable structures were located on the potential energy hypersurface of **IV**. Like **III**, **IV** also has two nonplanar forms, *E*-**IV**-*anti*3-[*anti*5] and *Z*-**IV**-[*syn*3]-*syn*5, in which the Me groups are out of the molecular plane by 65.8 and 65.4°, respectively. It should be noted that attempts to locate fully planar *E*-**IV**-*anti*3-[*anti*5] and/or *Z*-**IV**-[*syn*3]-*syn*5 forms by starting the geometry optimization by fully planar forms resulted to the previously derived nonplanar ones. The *Z*-**IV**-*anti*3-*syn*5 form is more stable than *E*-**IV**-*anti*3-*syn*5, *Z*-**IV**-[*syn*3]-*syn*5 and *E*-**IV**-*anti*3-[*anti*5] by 0.09, 1.19, and 1.64 kcal/mol, respectively. The substituent effect of the OMe group was not studied in Reference 10. Hence, comparisons for the global-minimum geometries derived cannot be made for either **III** or **IV**.

Unlike **I**, which has only one radical conformer, there are eight local minima on the potential energy hypersurface of the radicals of **II**, and four in those of **III** and/or **IV**. The most stable radical conformers of **I**, **II**, **III**, and **IV** are **V**, **XI**, **XII**, and **XIII**, respectively, which, along with selected structural data, are also shown in Figure 1.

Figure 1 shows the planar calculated optimized structures for the parent conformers and the phenoxyl radicals, which suggest good antioxidant activity as a result of complete conjugation. All parent compounds present the C–C bond alternation in the benzene ring; the respective radicals present a quinoid structure. Morever, the phenoxyl radical C–O bond lengths present a significant bond shortening of *ca.* 0.12 Å, as compared to those of the parent compounds. Values obtained range from 1.239 to 1.261 Å, and account well for a significant amount of double-bond character (1,3,13). All these features were also found (1) in the case of cinnamates and might account well for the correctness of our calculated radical structural parameters.

The formation of an intramolecular hydrogen bond in the parent **II**, **III**, and **IV** antioxidants, affording the *toward* conformer from an *away* one, is substantiated by the bond-length and bond-angle value differences (see also Fig. 1), also observed previously (1,3).

The nearly equal O–H bond-length values derived for all parent compounds (0.970–0.974 Å) could mean that, as expected (1,3,14), the O–H bond-length value is not a useful molecular descriptor by itself in comparing antioxidant activity of the phenolic antioxidants.

Vibrational frequencies. Owing to the lack of frequency information from IR and Raman spectra in the gas phase for all of the parent molecules, vapor phase frequency values of the most characteristic groups were compared with our calculated frequency values and found to closely match ours. The scaled [empirical factor of 0.9613 (1,3)] calculated stretching frequency values of the most important harmonic frequencies [$\nu(O–H)_{phen}$, $\nu(O–H)_{carb}$, and $\nu(C=O)$], shown in Table SII (available upon request from the author), are smaller than the available vapor phase ones and agree with them to ±3%. This could account well for the correctness of the calculated vibrational frequency values. The H-bond strength trend, **III** (4.70 kcal/mol) > **IV** (4.34 kcal/mol) = **II** (H-bond *via* the *meta*-OH group) > **II** (3.20 kcal/mol, H-bond *via* the *para*-OH group), calculated for the benzoates is the same as that of the homologous cinnamates. Moreover, in comparison with cinnamates, the homologous benzoates exhibit almost identical IR frequency values for $\nu(O–H)_{phen}$, whether H-bonded or not. However, they present slightly higher $\nu(O–H)_{phen}$ and $\nu(C=O)_{carb}$ values.

ΔHOF between the antioxidant and the respective radical. For the phenolic acid antioxidants, the radical mechanism for the hydrogen abstraction is generally accepted (14,15). Hence, ΔHOF values of the parent molecule–radical couples are shown in Table 1. Note the following features: (i) Each ΔHOF value corresponds to the radical involved in the parent molecule–radical couple used in the respective calculation; (ii) ΔHOF values of the homologous cinnamates are also presented; (iii) the radicals of **I**, **III**, and **IV**, used in the calculation of the benzoate

ΔHOF values, are **V**, **IX**, and **X**, respectively; and (iv) three different radical structures were considered for **II**, the benzoate homolog of the cinnamate, caffeic acid (1,3). The first two of there correspond to the radical structures deriving from the OH group at C(4), in which the intramolecular hydrogen bond is retained (**VI**) (see also Scheme 1 and Fig. 2) or eliminated (**VII**), and the third corresponds to the structure in which an $H^\bullet$ was eliminated from the OH group at C(3), leading also to the nonhydrogen-bonding structure (**VIII**).

In Table 1 the ΔHOF values of the *p*-hydroxybenzoic acid derivatives, ranging from *ca.* 305 to 345 kJ/mol, have energy differences in the range of *ca.* 3–19 kJ/mol. The significant energy differences between the ΔHOF values provide a way to order the structurally related compounds according to their antioxidant activity. The trend for ease of hydrogen atom abstraction, accounting for the antioxidant activity of the compounds, decreases as follows: **VI** > **X** > **IX** ≅ **V**. This theoretical antioxidant trend is in excellent agreement with the experimental one in lipid systems (16,17). Identical antioxidant-activity trends are derived by considering the same parent molecule–radical couples as those of cinnamates and/or those corresponding to our most stable parent-radical conformers. The corresponding ΔHOF values for **VI**, **X**, **IX**, and **V**, in ascending order, are much the same: 305.06 > 324.76 > 341.03 > 344.43 kJ/mol and 308.19 > 324.47 > 339.49 > 344.47 kJ/mol, respectively. This can be easily explained by considering the low calculated rotational barrier energies for the C_{phenyl}–$O_{hydroxyl}$ and C_{phenyl}–$C_{carboxyl}$ bonds (*vide supra*), allowing for easy rearrangement at room temperature. Moreover, global-minimum structures of all antioxidants exhibit the lowest dipole moment values compared to any other corresponding conformer. Calculated values are 1.99, 1.04, 1.74, and 0.37 D for **I**, **II**, **III**, and **IV**, respectively. This could help their dilution in lipid systems, mainly for **II** and **IV**, further facilitating further the hydrogen abstraction. All ΔHOF values of the *p*-hydroxybenzoic acid derivatives are larger than those of the cinnamates, accounting for a lower antioxidant activity. Differences in ΔHOF values are significant, amounting in most cases to *ca.* 12–17 kJ/mol, which provides a way to differentiate between those two structurally related families of compounds. Moreover, in a preceding section as well as in a previous paper (1), compounds of both benzoates and cinnamates were shown to be planar. Planarity of compounds strongly supports complete conjugation within parent and radical molecular species, accounting well for their stability. In addition, intramolecular H-bond interactions found in three out of the four members of both families further strengthen their stabilization. The only structural difference between the two families is an additional C=C bond in the side chain of the cinnamates, which has a stronger stabilizing effect by resonance on the phenoxyl radical (1). Moreover, this bond could affect the electronic effects of the two electron-withdrawing (EW) groups, –COOH and –CH=CHCOOH, in the benzoates and cinnamates, respectively. EW groups raise the O–H BDE; hence, they are not beneficial to enhance the antioxidant activity (18,19). However, –COOH is a much stronger EW group than –CH=CHCOOH, as evidenced by the Brown parameters (20), σ_p of their analogous –CH=CHCOOEt and –COOEt groups (+0.45 and +0.03, respectively). Consequently, benzoates are expected to be less active than cinnamates. Calculated Δ[ΔHOF] values, estimated as Δ[ΔHOF] = (ΔHOF_{benz} – ΔHOF_{phen}) and = (ΔHOF_{cinn} – ΔHOF_{phen}), for the benzoates and cinnamates, respectively (see also Table 1), could provide further support for this. Additional calculations performed on the homologous simple phenols, from which the –COOH and –CH=CHCOOH groups were eliminated, afforded Δ[ΔHOF] values in close agreement with the above predictions. Δ[ΔHOF] values for the benzoates were positive, accounting for higher O–H BDE compared to the simple phenols and hence for lower antioxidant activity. The opposite holds true for the Δ[ΔHOF] values of cinnamates. Consequently, our theoretical ΔHOF values indicate that the elimination of an ethylenic group from the –CH=CH-COOH side chain of a phenyl ring carrying a *p*-hydroxy group has an unfavorable effect on the antioxidant activity, also in excellent agreement with experimental values (16,17). Natella *et al.* (17) compared the experimental antioxidant activity of the four derivatives of benzoic acid under investigation and their homologous derivatives of cinnamic acid. Substitution of the carboxylic group of the benzoic acid derivative by the propenoic side chain, leading to the homologous cinnamic acid derivative, enhanced the antioxidant capacity of the aromatic ring considerably. The antioxidant efficiency of monophenols was also strongly enhanced by the introduction of a second hydroxy group and was increased further by one or two methoxy substitutions in positions *ortho* to the OH group.

Spin density values. Figure 3 shows the computed spin density values of the atoms constituting the radicals of the antioxidants studied. On the COOH group the spin density is very low, becoming zero in the case of the radical **VIII**. Hence, almost all spin remains in the benzene ring and the oxygen atoms of its substituents. This, along with the planarity of all of the radicals, leads to their full conjugation and to a moderate spin delocalization. Consequently, the lower antioxidant activity of benzoates, relative to cinnamates, could be due to their (i) lower spin delocalization, (ii) higher calculated ΔHOF values, and (iii) a stronger electron-withdrawing effect, associated with the –COOH group relative to –CH=CHCOOH. Moreover, the absence of a high amount of localized spin in the antioxidants studied may diminish the possibility of initiating a radical chain reaction (21).

Highest occupied molecular orbital (*HOMO*) *eigenvalues.* Molecular electron-donating ability is characterized by the parameter HOMO; the lower the HOMO eigenvalue, the lower the antioxidant activity of a molecule (1,3). The computed HOMO eigenvalues of **I** to **IV** antioxidants are –0.2498, –0.2389, –0.2335, and –0.2229 au, respectively. *p*-Hydroxybenzoic acid, having the lowest antioxidant activity, exhibits the lowest HOMO eigenvalue. However, protocatechuic acid, despite having the highest antioxidant activity, has the second-lowest HOMO eigenvalue; on the basis of the antioxidant activity trend already derived, the vanillic acid HOMO eigenvalue should lie between protocatechuic and *p*-hydroxybenzoic

TABLE 1
ΔHOF Values of the Benzoic Phenoxy Radicals and Those of Their Cinnamate and Simple Phenol Homologs

Phenoxy radical	Hr[a]	Hm[b,c]	ΔHOF[d]	ΔHOF[e]	ΔHOF[f]	Δ(ΔHOF)[g]	ΔHOF[h]	Δ[ΔHOF][i]	Δ[ΔHOF][j]
V	−495.299173	−495.928264	82.32	344.41	326.97	17.4	333.16	11.25	−6.19
VI	−570.529502	−571.143607	72.91	305.06	291.56	13.5	296.72	8.34	−5.16
IX	−609.792359	−610.420168	81.51	341.04	328.77	12.3	332.20	8.84	−3.43
X	−724.283421	−724.904770	77.46	324.08	308.66	15.4	316.59	7.49	−7.93
VII	−570.515938	−571.143607	81.44	340.68	327.91	12.8	—	—	—
VIII	−570.515917	−571.143607	81.42	340.73	338.70	2.0	—	—	—

[a] Sum of electronic and thermal enthalpy of phenoxy radicals in Hartrees.
[b] Sum of electronic and thermal enthalpy of parent molecules in Hartrees.
[c] The sum of electronic and thermal enthalpy of the H atom is −0.497912 Hartrees.
[d] Heat of formation (ΔHOF) values of the *p*-hydrobenzoic acid derivatives in kcal/mol.
[e] ΔHOF values of the *p*-hydrobenzoic acid derivatives in kJ/mol.
[f] ΔHOF values of the *p*-hydroxycinnamic acids in kJ/mol.
[g] Δ(ΔHOF) has been estimated as Δ(ΔHOF) = (ΔHOF[e] – ΔHOF[f]) in kJ/mol.
[h] ΔHOF values (in kJ/mol) of the phenol (333.16), catechol-*toward* (296.72), guaiacol (332.2), and syringol (316.59).
[i] Δ[ΔHOF] has been estimated as Δ[ΔHOF] = (ΔHOF[e] - ΔHOF[h]) (in kJ/mol).
[j] Δ[ΔHOF] has been estimated as Δ[ΔHOF] = (ΔHOF[f] – ΔHOF[h]) (in kJ/mol).

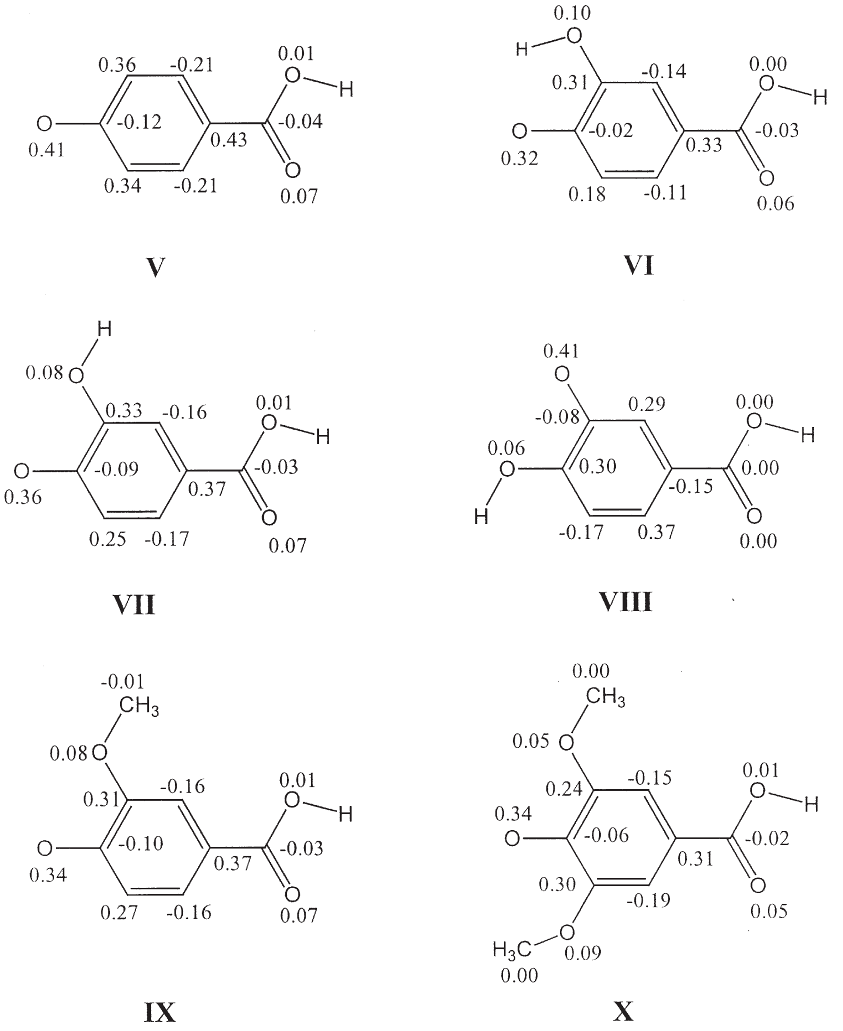


FIG. 3. Computed spin density values of the atoms constituting the radicals of the antioxidants studied. Only values of ≥0.01 are shown; the benzene ring hydrogens, possessing 0.01 spin values, are omitted for clarity.

acids. As with cinnamates, HOMO eigenvalue differences are not suitable for predicting antioxidant activity. Furthermore, with the exception of the syringic–sinapinic homolog, all cinnamates exhibit higher HOMO eigenvalues than those of their benzoate homolog. Although the HOMO eigenvalue difference between the two homologous syringic and sinapinic acids is small (0.0007 au), the HOMO eigenvalue–antioxidant activity correlation rule seems to hold true only for three out of the four antioxidant couples studied. Hence, it also appears that HOMO eigenvalue differences are not suitable to differentiate the antioxidant activity between those two series of structurally related compounds.

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