# A Density Functional Theory Study of Structure–Activity Relationships in Caffeic and Dihydrocaffeic Acids and Related Monophenols

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**ABSTRACT:** Structure–activity relationships in the antioxidants caffeic acid and dihydrocaffeic acid as well as in the monophenols isoeugenol, eugenol, and dihydroeugenol were investigated by using the density functional theory (DFT). The higher antioxidant activity of caffeic acid, among the rest, could be attributed to its lower difference in the heat of formation (ΔHOF) value. Dihydrocaffeic acid exhibits less antioxidant activity than caffeic acid, owing to both its higher ΔHOF value and its limited spin delocalization. These two latter findings could also account for the lower antioxidant activity of both eugenol and dihydroeugenol as compared to isoeugenol. DFT calculations afford a good molecular descriptor, ΔHOF, that correlates well with the antioxidant activity in molecules exhibiting similar structural characteristics. The presence of a simple double bond in the side chain makes a difference in the antioxidant activity only if it leads to an extended conjugation. Calculated dipole moment values for both the parent molecules and the respective phenoxyl radicals correlate well with their antioxidant efficiency in some instances.

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**KEY WORDS:** Antioxidant, B3LYP, caffeic acid, DFT, dihydrocaffeic acid, dihydroeugenol, eugenol, ferulic acid, ΔHOF, isoeugenol, structure–activity relationships.

The capacity to predict antioxidant activity is important, because it improves the selection of effective new compounds with low toxicity and saves experimental work. The interest in the relative evaluation of antioxidants (AH) through theoretical calculations is increasing, and several molecular descriptors have been used so far in an attempt to find suitable theoretical parameters characterizing the activity of the antioxidants (1–6). The main mechanism of action by phenolic antioxidants (AH) is considered to be the scavenging of free radicals by donation of their phenolic hydrogen atom (7). Parameters that characterize this ease of donation could be useful in estimating the ability of phenolic compounds to scavenge free radicals. A molecular descriptor that seems to correlate well with experimental results is the difference in the heat of formation (ΔHOF) values between the parent molecule (AH) and its corresponding radical ($R^\bullet$) (2–4,8), also denoted as the phenolic O–H bond dissociation enthalpy (BDE). Calculations used for the determination of ΔHOF and other theoretical parameters are mostly semiempirical. However, continuing improvements in computer technology and electronic structure calculation software allow us to compute modest-sized molecules at "state-of-the-art" *ab initio* and/or density functional theory (DFT) levels in reasonable times.

In the present study, differences in the activity of the compounds examined in Reference 9 were studied on a theoretical basis. In particular, it was shown that the experimental differences found for caffeic acid and its saturated counterpart as well as for eugenol, isoeugenol, and dihydroeugenol were strongly dependent on conditions that influenced the order and size of this difference. Quantum-chemical calculations were used to examine whether molecular characteristics support the experimental findings (9). To the best of our knowledge, neither experimental X-ray nor theoretical structural and/or energetic parameters are available for four out of the five compounds studied. These parameters are available, however, for four cinnamic acid derivatives, including caffeic acid, studied by using both *ab initio* and DFT calculations (8). It was shown that the Lee–Yang–Parr correlational functional theory (B3LYP)-calculated ΔHOF is a meaningful molecular descriptor of antioxidant activity in accordance with experimental data. Hence, DFT/B3LYP calculations, with the same basis set, were carried out in the present study for comparison. Calculations resulted in optimization of the geometries of the antioxidants and their respective phenoxyl radicals, determination of their vibrational frequencies, and evaluation of the corresponding ΔHOF values, dipole moment values, highest occupied molecular orbital (HOMO) eigenvalues, and spin density values.

## THEORETICAL METHODS

The geometries of all minimum energy structures for the parent molecules were fully optimized by employing DFT calculations, using the Becke's 3 parameter hybrid functional, using the Lee–Yang–Parr correlational functional theory (B3LYP) and UB3LYP (unrestricted B3LYP) for their corresponding radicals with the 6-31+G(d) basis set, as detailed before (8). All calculations were carried out using the GAUSSIAN 98 program suite (10).

The total enthalpy of each parent molecule at 298 K is the sum of the thermal correction to the enthalpy and the B3LYP energy. To form the radical, an $H^\bullet$ was removed from the

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phenolic hydroxyl group in each parent molecule. The enthalpy at 298 K of each radical is the sum of the thermal correction to the enthalpy and the UB3LYP energy. In the calculations of the ΔHOF, the enthalpy of the H-atom at 298 K was used. The thermal correction to the enthalpy in the GAUSSIAN 98 program includes the zero-point energy.

ΔHOF is calculated as the 298 K theoretical enthalpy difference for the reaction:

$$\mathrm{ArOH} \rightarrow \mathrm{ArO}^{\bullet} + \mathrm{H}^{\bullet} \qquad [1]$$

where ArOH, $\mathrm{ArO}^{\bullet}$, and $\mathrm{H}^{\bullet}$ are the parent phenol, its corresponding radical, and the H atom radical, respectively.

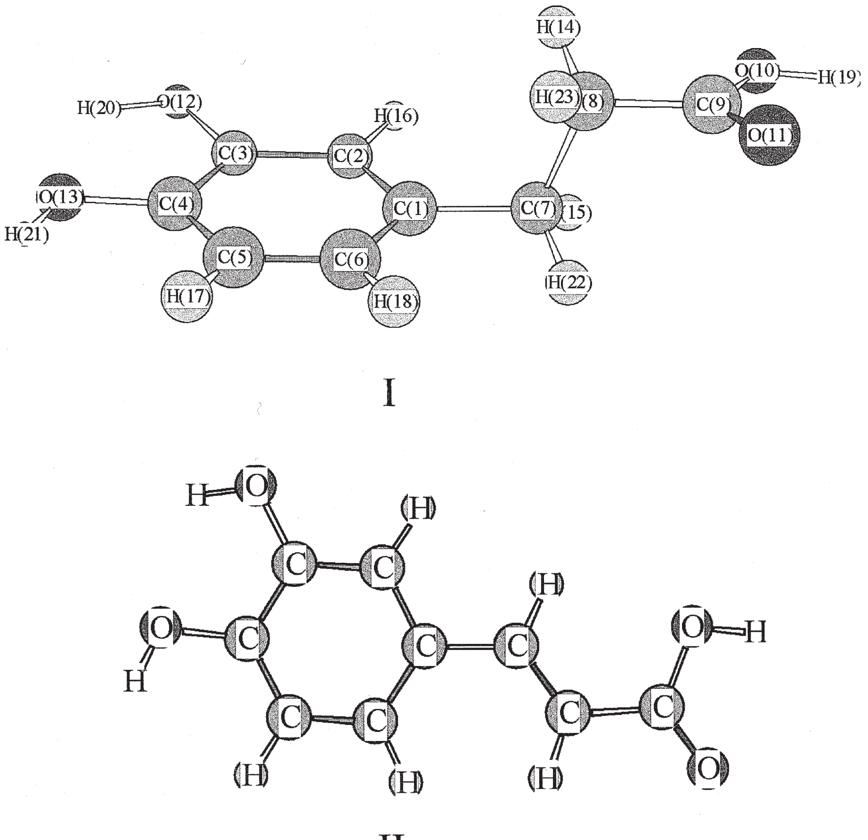
The above methodology is similar to the "full basis calculation of BDE" method applied by Wright *et al.* (11), which yielded ΔHOF values identical to those derived by the methodology used in our previous paper (8). Contrary to Wright *et al.*, the geometries of the parent molecules and the respective radicals were derived, in our case, by using the B3LYP instead of the Austin Model 1 (AM1) method.

The most probable structure of an antioxidant molecule in solution is the one favoring the formation of intermolecular hydrogen bonds; the one adopting intramolecular hydrogen bonding is the most probable in the gas phase and/or in very dilute solutions. Hence, for a complete study, two different structural conformations were considered for all parent compounds. In the first one the intramolecular hydrogen bond was retained (hereafter denoted as *toward*); in the second the hydrogen bond was eliminated (hereafter denoted as *away*).

## RESULTS AND DISCUSSION

A good knowledge of the geometries of the antioxidants and their respective phenoxyl radicals being considered is necessary for a complete theoretical study; still, neither the structures nor the vibrational frequencies of four out of the five compounds discussed in this paper have been studied theoretically and/or experimentally. Therefore, phenolic O–H bond length was the first "structural" molecular descriptor considered. In a subsequent stage a comparison was attempted between the calculated "energetic" ΔHOF values and the experimental results. Moreover, other molecular descriptors, such as the dipole moment values, the HOMO eigenvalues, and the spin density values, were considered.

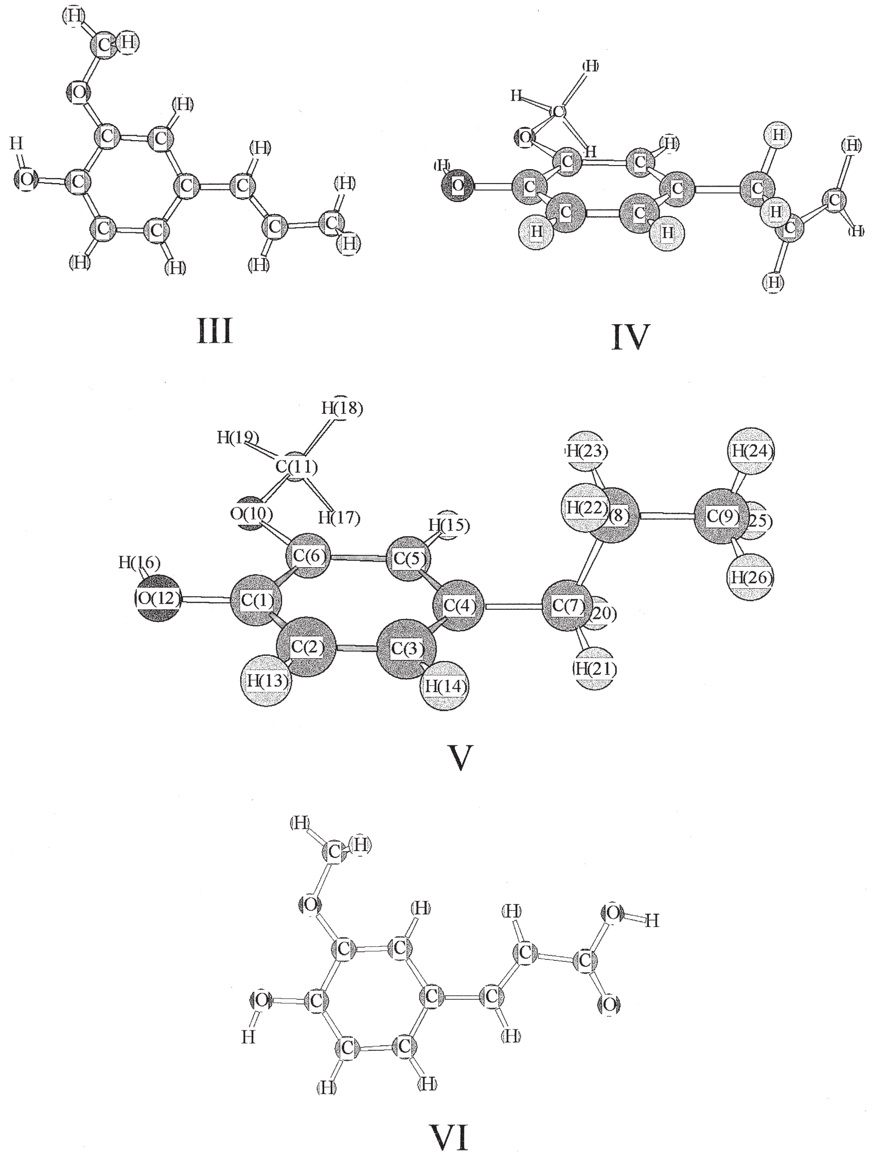
*Equilibrium geometries*. The resulting optimized structures for **I** (dihydrocaffeic acid), **II** (caffeic acid), **III** (isoeugenol), **IV** (eugenol), and **V** (dihydroeugenol), together with the adopted numbering schemes, are given in Schemes 1 and 2, respectively. The corresponding structure of **VI** (ferulic acid) (8), studied earlier, is also shown in Scheme 2, since this is a planar, benzene-ring substituted analog (hereafter denoted as *analog*) of **III**, **IV**, and **V**. It should be stressed that both *away* and *toward* conformations of the **III**, **IV**, and **V** parent compounds afford identical respective radicals, being the **III-r** (isoeugenol radical), **IV-r** (eugenol radical), and **V-r** (dihydroeugenol radical). However, three different radical structures were considered for **I** for purposes of comparison to its planar *analog*, **II**, which was studied previously (8). The first two correspond to



I

II

SCHEME 1



**SCHEME 2**

the radical structures deriving from the OH group at C(4), in which the intramolecular hydrogen bond is retained (**VII**, dihydrocaffeic acid H-bonded radical) or eliminated (**VIII**, dihydrocaffeic acid non-H-bonded radical), and the third to the structure in which an $H^\bullet$ is eliminated from the OH group at C(3) (**IX**, dihydrocaffeic acid opposite radical), leading also to a nonhydrogen-bonding structure (Schemes 1,2).

Schemes 1 and 2 clearly show that, contrary to the planar optimized structure derived for **II** and **III**, those of **I**, **IV**, and **V** are 3-D ones. Actually, due to the $sp^3$ hybridization on C(7), all of the methylcarboxy, ethyleno, and/or ethyl edge-fragments of **I**, **IV**, and **V**, respectively, lie out of the benzene-ring plane. In particular, the 3-D structures of **V** and **I** present a staggered conformation around the connecting C(7)–C(8) bonds. This accounts well for the correctness of our results, since a staggered conformation leads, in general, to a more energetically stable structure than an eclipsed one. Moreover, contrary to the edge-fragments in **I** and **V**, lying on a perpendicular to the benzene-ring plane, and in the projection of the C(4)–C(1)–C(7) line (thus forming a C(4)–C(7)–C(8)–C(9) dihedral angle value of 180°), that of **IV** is only 123.0° (Table 1). This structural conformation of **IV** derives mainly from rotation around the C(7)–C(8) bond. However, the same optimized structure was derived upon repeating a full B3LYP/6-31+G(d) optimization for **IV** with an initial C(4)–C(7)–C(8)–C(9) angle value of 180°. This structural staggered-like preference of **IV** could be the result of stabilization through hyperconjugation (12). This was further substantiated by performing additional single-point calculations on alternative conformations, generated by rotation about the C(4)–C(7) bond. Rotations of 10, 20, 30, and 40° resulted in an energy increase of 0.26, 0.50, 0.92, and 1.42 kcal/mol, respectively. A $C_1$ symmetry point group was assumed for all 3-D-structured compounds.

The substituted phenyl ring and the methyl group in the optimized planar structure of **III** are *trans* to each other around the connecting carbon-carbon double bond. This could account well for the correctness of our results, since a *trans* configuration leads, in general, to a more energetically

**TABLE 1**
**Comparison of Selected Structural Parameters at the Optimized Geometries for I and II**

| Structural parameter | **I**-*toward* | **II**-*toward* |
|---|---|---|
| R (C1–C2)[a,b,c] | 1.403 | 1.409 |
| R (C2–C3) | 1.393 | 1.390 |
| R (C3–C4) | 1.404 | 1.404 |
| R (C4–C5) | 1.391 | 1.396 |
| R (C5–C6) | 1.400 | 1.393 |
| R (C6–C1) | 1.400 | 1.408 |
| R (C1–C7) | 1.514 | 1.463 |
| R (C7–C8) | 1.553 | 1.351 |
| R (C8–C9) | 1.512 | 1.468 |
| R (O13–H21) | 0.969 | 0.969 |
| R (O12–H20) | 0.973 | 0.973 |
| R (C3–O12)[d,e,f] | 1.366 | 1.365 |
| R (C4–O13)[d,e,f] | 1.381 | 1.375 |
| R (C9–O11) | 1.214 | 1.220 |
| R (C9–O10) | 1.361 | 1.365 |
| R (C5–H17) | 1.089 | 1.089 |
| R (C7–H15) | 1.096 | 1.088 |
| θ (C2–C3–C4) | 119.6 | 119.4 |
| θ (C3–C4–C5) | 120.1 | 120.2 |
| θ (C4–C5–C6) | 119.9 | 120.1 |
| θ (C4–O13–H21) | 110.6 | 110.9 |
| θ (C3–O12–H20) | 108.5[g] | 108.8 |
| θ (C2–C1–C7) | 120.3 | 118.2 |
| θ (C1–C7–C8) | 112.1 | 127.4 |
| θ (C7–C8–C9) | 111.2 | 123.9 |
| θ (C2–C3–O12) | 119.7[g] | 119.7 |
| θ (C3–C4–O13) | 115.1[g] | 115.2 |
| θ (C4–C3–O12) | 120.7[g] | 120.8 |
| θ (C5–C4–O13) | 124.8 | 124.6 |
| θ (C8–C9–O10) | 112.1 | 114.3 |
| θ (C8–C9–O11) | 125.8 | 124.2 |
| D (C1–C7–C8–C9) | 178.3 | 180.0 |
| D (C6–C1–C7–C8) | 88.0 | 000.0 |

[a] All bond lengths in Å. **I**, dihydrocaffeic acid; **II**, caffeic acid; **III**, isoeugenol; **IV**, eugenol; **V**, dihydroeugenol; **VII**, dihydrocaffeic acid H-bonded radical; **VIII**, dihydrocaffeic acid non-H-bonded radical; **IX**, dihydrocaffeic acid opposite radical.

[b] All bond and dihedral angles in degrees.

[c] R, θ, and D stand for bond lengths, bond angles, and dihedral angles, respectively.

[d] C3–O12 and C4–O13 bond lengths in the corresponding hydrogen bonding, **VII** radicals are 1.337, 1.260 and 1.337, 1.253 Å for **I** and **II**, respectively.

[e] C3–O12 and C4–O13 bond lengths in the corresponding nonhydrogen bonding, **VIII** radicals are 1.252, 1.347 and 1.243, 1.347 Å for **I** and **II**, respectively.

[f] C3–O12 and C4–O13 bond lengths in the corresponding nonhydrogen bonding, **IX** radicals are 1.252, 1.348 and 1.252, 1.343 Å for **I** and **II**, respectively.

[g] The corresponding C3–O12–H20, C2–C3–O12, C3–C4–O13, and C4–C3–O12 angle values for **I**-*away* are 109.5, 123.3, 117.3, 117.1, and 123.7°, respectively.

**TABLE 2**
**Comparison of Selected Structural Parameters at the Optimized Geometries for III, IV, V, and VI**

| Structural parameter | **III**-*toward* | **IV**-*toward* | **V**-*toward* | **VI**-*toward* |
|---|---|---|---|---|
| R (C1–C2)[a,b,c] | 1.393 | 1.389 | 1.390 | 1.391 |
| R (C2–C3) | 1.395 | 1.401 | 1.400 | 1.396 |
| R (C3–C4) | 1.405 | 1.397 | 1.399 | 1.410 |
| R (C4–C5) | 1.412 | 1.408 | 1.408 | 1.416 |
| R (C5–C6) | 1.392 | 1.392 | 1.394 | 1.386 |
| R (C6–C1) | 1.407 | 1.410 | 1.409 | 1.416 |
| R (C4–C7) | 1.472 | 1.523 | 1.515 | 1.458 |
| R (C7–C8) | 1.344 | 1.501 | 1.543 | 1.351 |
| R (C8–C9) | 1.502 | 1.337 | 1.533 | 1.469 |
| R (C1–O12)[d] | 1.366 | 1.367 | 1.368 | 1.359 |
| R (O12–H16) | 0.973 | 0.973 | 0.973 | 0.974 |
| R (C6–O10) | 1.377 | 1.377 | 1.378 | 1.373 |
| R (C11–O10) | 1.423 | 1.422 | 1.421 | 1.424 |
| R (C2–H13) | 1.086 | 1.086 | 1.086 | 1.086 |
| R (C7–H20) | 1.092 | 1.099 | 1.100 | 1.090 |
| R (C9–H24) | 1.099 | 1.099 | 1.097 | 1.097 |
| θ (C1–C2–C3) | 120.4 | 120.0 | 120.0 | 119.8 |
| θ (C5–C6–C1) | 120.2[e] | 120.4[f] | 120.3[g] | 120.4[h] |
| θ (C6–C1–C2) | 119.3 | 119.4 | 119.4 | 119.7 |
| θ (C4–C7–C8) | 128.0 | 113.6 | 113.6 | 128.1 |
| θ (C7–C8–C9) | 124.5 | 125.1 | 112.9 | 120.4 |
| θ (C5–C6–O10) | 125.9[e] | 125.8[f] | 125.9[g] | 126.1[h] |
| θ (C1–C6–O10) | 113.9[e] | 113.8[f] | 113.9[g] | 113.5[h] |
| θ (C6–C1–O12) | 120.6[e] | 120.4[f] | 120.4[g] | 120.2[h] |
| θ (C1–O12–H16) | 107.9[e] | 107.9[f] | 107.9[g] | 108.2[h] |
| θ (C2–C1–O12) | 120.1[e] | 120.2[f] | 120.1[g] | 120.2[h] |
| D (C4–C7–C8–C9) | 180 | 123.0 | 180 | 180 |
| D (C5–C4–C7–C8) | 180 | 123.6 | 84.1 | 0 |

[a,b,c] See Table 1, footnotes *a,b,c*.

[d] The C1–O12 bond length in the corresponding **III-r**, **IV-r**, **V-r**, and **VI-r** radicals is 1.246, 1.251, 1.252, and 1.242 Å, respectively.

[e] The corresponding C5–C6–O10, C1–C6–O10, C6–C1–O12, C1–O12–H16, and C2–C1–O12 angle values for **III**-*away* are 125.1, 115.8, 117.4, 109.2, and 123.4°, respectively.

[f] The corresponding C5–C6–O10, C1–C6–O10, C6–C1–O12, C1–O12–H16, and C2–C1–O12 angle values for **IV**-*away* are 125.1, 115.6, 117.2, 109.2, and 123.5°, respectively.

[g] The corresponding C5–C6–O10, C1–C6–O10, C6–C1–O12, C1–O12–H16, and C2–C1–O12 values for **V**-*away* are 125.1, 115.7, 117.3, 109.1, and 123.4°, respectively.

[h] The corresponding C5–C6–O10, C1–C6–O10, C6–C1–O12, C1–O12–H16, and C2–C1–O12 angle values for **VI**-*away* are 125.3, 115.3, 116.9, 109.5, and 123.4°, respectively. **VI**, ferulic acid; for other symbols see Table 1.

stable structure than a *cis* one. The planar-calculated optimized structures for the parent *toward* and *away* conformations of both **III** and **II** and their respective radicals imply that these molecules are completely conjugated. These observations could suggest that the two latter compounds have a better antioxidant activity in comparison to those of **I**, **IV**, and **V** (*vide infra*). Planar structures also were derived for the substituents OH and OMe, in all calculated planar and 3-D optimized structures, in excellent agreement with our previous findings (8) for a series of four *analogs*, namely, the substituted *p*-hydroxycinnamic acids and the assumptions made by Wu *et al.* (13).

Selected structural parameters at the optimized geometries for the *toward* and *away* conformations of the parent **I**, antioxidant, and its radicals are given in Table 1; Table 2 presents the corresponding values for **III**, **IV**, and **V**. Owing to the lack of X-ray structural as well as theoretical data for all of the above compounds, the theoretical structural parameters of their *analogs*, **II** and **VI** (8), are given for comparison in Tables 1 and 2, respectively. An inspection of both tables shows that, with few exceptions, the corresponding computed structural parameters agree within 1.5% or better. All structural parameters lie within the observed range already derived (8) for **II** and **VI**. Moreover, all parent compounds present the C–C bond alternation in the benzene ring; the respective radicals present a quinoid structure. All these were also found by us (8), in the case of **II** and **VI** antioxidants, and by Wu *et al.* (13)

and account well for the correctness of our calculated structural parameters. The hydrogen-bonded phenolic O–H bond-length values in all parent *toward* compounds studied are identical to each other (0.973 Å) and only 0.003 Å longer than those of the non-hydrogen-bonded ones in the *away* conformations. The equal values derived for each separate set of these bonds could mean that the O–H bond-length value is not a suitable molecular descriptor by itself, to compare antioxidant activity of phenolic antioxidants. Zhang (3) reached a similar conclusion, as did we (8).

Formation of an intramolecular hydrogen bond in the parent **III**, **IV**, and **V** antioxidants, affording the *toward* conformer from an *away* one, is substantiated mainly by the increase (by *ca.* 3.0°) of the C(6)–C(1)–O(12) bond angles, followed by a concomitant decrease of the C(1)–C(6)–O(10) (by *ca.* 2.0°), C(1)–O(12)–H(16) (by *ca.* 1.0°), and C(2)–C(1)–O(12) (by *ca.* 3.0°) values; **I** presents angle-value differences that are analogous to those of **III**, **IV**, and **V**. A possible rationale for these differences was given in a previous paper (8). The phenoxyl radical C–O bond lengths, given in the footnotes of Tables 1 and 2, present a significant bond shortening of *ca.* 0.12 Å, as compared to those of the parent compounds. In particular, values obtained range from 1.242 to 1.260 Å, in close agreement with a significant amount of double-bond character (8,14).

*Vibrational frequencies*. Frequency information from IR and Raman spectra in the gas phase was not available for any of the molecules under study. Vapor phase frequency values (15,16) of the most characteristic groups closely match the calculated ones of the antioxidants under study. The most important harmonic frequencies, $\nu(\text{O–H})_{\text{phenyl}}$, $\nu(\text{O–H})_{\text{carboxyl}}$, and $\nu(\text{C=O})$, of the antioxidants studied were chosen on the basis of the importance of the bond represented and the intensity of the corresponding absorption, as described elsewhere (8). The foregoing frequencies are well characterized as stretch bands, since both the molecular geometry and eigenvector orientation of these atoms lie on a single plane. The harmonic oscillator approach, which is often used for the calculated frequencies, usually produces higher values than the fundamental ones. Therefore, it is usual to scale frequencies predicted at the B3LYP model of DFT level of theory by an empirical factor of 0.9613 (17). All scaled calculated frequency values, $\nu(\text{O–H})_{\text{phenyl}} = 3552–3621\ \text{cm}^{-1}$, $\nu(\text{O–H})_{\text{carboxyl}} = 3532–3556\ \text{cm}^{-1}$, and $\nu(\text{C=O}) = 1710–1745\ \text{cm}^{-1}$, are smaller than the available vapor phase values of $\nu(\text{O–H})_{\text{phenyl}} = 3651\ \text{cm}^{-1}$, $\nu(\text{O–H})_{\text{carboxyl}} = 3582\ \text{cm}^{-1}$, and $\nu(\text{C=O}) = 1762\ \text{cm}^{-1}$, and within 3% or better agreement. This could well account for the correctness of the calculated vibrational frequency values. In particular, the phenolic O–H stretching frequencies of the *toward* conformations appear in the region of 3552 to 3621 $\text{cm}^{-1}$; those in the *away* ones appear at 3608 $\text{cm}^{-1}$. Moreover, the formation of an intramolecular hydrogen bond (*toward* conformation) in **I** to **VI** leads to a weakening of the O–H bond participating in the hydrogen bond (shift toward lower frequency values, ranging from 3563 to 3574 $\text{cm}^{-1}$), as compared to that in the *away* conformation. Additionally, in the case of **I** and **II** antioxidants, which have two adjacent phenolic O–H groups, a concomitant strengthening of the second, free O–H bond is also observed (shift toward higher-frequency values of 3621 and 3616 $\text{cm}^{-1}$, respectively), followed by a simultaneous narrowing of both bands. This narrowing is further substantiated by its frequency intensity A [= 77.6 and 106.1 (arbitrary units), respectively], since high-frequency intensity results in a narrow absorption bandwidth. All these are in line with the facts that hydrogen bond formation increases the IR intensity and decreases the O–H stretching frequency (16). Furthermore, it is well known that the stronger the hydrogen bond, the larger the OH stretching frequency shift toward a lower value (16). Hence, the hydrogen-bond strength does not differ in the case of the three monophenols, [$\nu(\text{O–H})_{\text{phenyl}} = 3563\ \text{cm}^{-1}$], whereas **I** has a higher hydrogen-bond strength [$\nu(\text{O–H})_{\text{phenyl}} = 3569\ \text{cm}^{-1}$] than **II** [$\nu(\text{O–H})_{\text{phenyl}} = 3574\ \text{cm}^{-1}$]. Finally, the scaled calculated carboxylic O–H stretching frequency values (3532–3556 $\text{cm}^{-1}$) are always lower than the scaled phenolic ones (3616–3621 $\text{cm}^{-1}$); still, the differences between the carboxylic carbonyl C=O group stretching bands (1710–1745 $\text{cm}^{-1}$) for all acids are not large.

*Heat of formation, ΔHOF between the antioxidant and the respective radical.* If the radical mechanism for hydrogen abstraction is taken into account, the ΔHOF of the parent molecule–radical couples should be considered. The calculated ΔHOF values of all antioxidants studied, along with that of **VI**, are shown in Table 3. Since **I** and **II** produce quite analogous radicals, all of them are labeled with the same symbols; however, the radicals generated by **II** are in parentheses.

Values in Table 3, ranging from 291 to 338 kJ/mol, clearly indicate that the *away* conformations of all compounds have lower ΔHOF values than the respective *toward* ones. This should be expected, because the *away* conformations are less energetically stable than the *toward* ones in the gas phase. Although this could account for relatively easier hydrogen atom abstraction for the former, comparisons will be made between the latter conformations of the antioxidants because of their greater stability in the gas phase and in very dilute solutions. Based on the same results, both **VII** and **VIII** radicals of **II** exhibit lower ΔHOF values than the corresponding ones of **I** by *ca.* 4 kJ/mol. It should be stressed here that radical **IX** of **I** should also exhibit higher ΔHOF values than that of **II**; its lower value is possibly due to structure conformational reasons. Actually, although in both **VII** and **VIII** radicals of **I** the COOH plane is parallel to the benzene ring, in the case of **IX** it forms a dihedral angle of 144° with the latter ring. It was also shown that the configuration of **IX**, in which the COOH plane is perpendicular to the benzene plane, yields a much lower ΔHOF value (331 kJ/mol). Hence, **II** exhibits a relatively easier tendency for hydrogen atom abstraction than **I**; their corresponding ΔHOF is small (*ca.* 4 kJ/mol). As far as antioxidants **III**–**V** are concerned, the first has a lower value (*ca.* 315 kJ/mol) than the other two, accounting for their relatively greater ability to donate a hydrogen atom. **IV** and **V** have almost equal values, and **IV** and **VI** exhibit almost identical ΔHOF values (*ca.* 328.5 kJ/mol). Schemes 1 and 2 clearly show that only **II** and **III** of the five antioxidants studied have planar structures. Structure planarity strongly supports complete conjugation within the parent and radical

**TABLE 3**
**ΔHOF Values of the *toward* and *away* Conformations of the Antioxidants Studied; Caffeic and Ferulic Acids and Their Respective Radicals**

| Antioxidant | Hr[a] | Hm[b,c] | ΔHOF[d] | ΔHOF[e] |
|---|---|---|---|---|
| **III**-*toward* | −537.892038 | −538.510172 | 75.44 | 315.64 |
| **III**-*away*[f] | −537.892038 | −538.502985 | 70.93 | 296.77 |
| **IV**-*toward* | −537.877529 | −538.500524 | 78.49 | 328.41 |
| **IV**-*away* | −537.877529 | −538.493342 | 73.98 | 309.55 |
| **V**-*toward* | −539.089011 | −539.711098 | 77.92 | 326.02 |
| **V**-*away* | −539.089011 | −539.703999 | 73.47 | 307.38 |
| **VI**-*toward* | −687.165329 | −687.788461 | 78.58 | 328.77 |
| **VI**-*away* | −687.165329 | −687.781084 | 73.95 | 309.40 |
| **VII** | −649.097288 | −649.707369 | 70.38 | 294.50 |
| **VIII** | −649.083374 | −649.707369 | 79.12 | 331.03 |
| **IX** | −649.081686 | −649.707369 | 79.44 | 335.00 |
| (**VII**) | −647.902003 | −648.510964 | 69.68 | 291.56 |
| (**VIII**) | −647.888156 | −648.510964 | 78.37 | 327.91 |
| (**IX**) | −647.884049 | −648.510964 | 80.95 | 338.70 |

[a] Sum of electronic and thermal enthalpy of phenoxyl radical in Hartrees.
[b] Sum of electronic and thermal enthalpy of parent molecule in Hartrees.
[c] The sum of electronic and thermal enthalpy of the H atom is −0.497912 Hartree.
[d] ΔHOF values in kcal/mol.
[e] ΔHOF values in kJ/mol.
[f] ΔHOF values for the *away* conformations are calculated by using the sum of electronic and thermal enthalpy values of the *away* parents in the corresponding formula.

molecular species. Moreover, intramolecular H-bond interactions found in all antioxidants under study further stabilize these molecules. All these are in close agreement with the antioxidant activity trends derived experimentally for **I** and **II**, as well as for the monophenols **III** to **V**, on the basis of the overall kinetics data for scavenging 1,1-diphenyl-2-picrylhydrazyl ($\text{DPPH}^{\bullet}$). In considering the overall kinetics data for the monophenols, isoeugenol was found more efficient by *ca.* 50 times than **IV** and **V**. On the contrary, the small difference between **I** and **II** was reflected in their ΔHOF value differences. The ΔHOF value difference between **III** and **IV** is *ca.* four times larger than that of the two diphenols (*ca.* 13 vs. 4 kJ/mol). ΔHOF values are usually in line with the antioxidant activity in bulk oils (8). However, in our case, this was observed only in the case of monophenols, whereas for the diphenols under study results were opposite.

It was also shown in the experimental work (9) that the 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) radical [$\text{ABTS}^{\bullet+}$] experimental results contradicted those of the $\text{DPPH}^{\bullet}$ radical. The scavenging mechanism of the $\text{ABTS}^{\bullet+}$ radical has not been elucidated yet. However, if the antioxidant mechanism for the $\text{ABTS}^{\bullet+}$ radical, suggested by Miller *et al.* (18), is taken into account, it should be expected that, owing to both their higher conjugation and planarity, **II** would exhibit higher activity than **I**, and **II** would exhibit higher activity than **IV** and **V**. Moreover, the same authors found that the presence of hydroxyl groups in the terminal rings of a conjugated chain significantly decreased the antioxidant activity. As a result, and based on our experimental findings, it seems probable that the effect of the hydroxyl groups in the terminal rings on the antioxidant activity of the planar antioxidants is greater than those of the respective 3-D ones. Moreover, ΔHOF values cannot highlight the performance of the compounds in the bulk oils and dispersed systems. For this reason, other molecular descriptors were also considered.

*Dipole moment values.* The dipole moment values for the antioxidants under study are given in Table 4. An inspection of those values clearly shows that, in each molecule, there is a consistent increase going from the *away* to the *toward* parent conformations, and finally to the radicals. In either case, the corresponding values are at least double; the two exceptions are the planar **II** and **VI** acids of which the *toward* value is higher than that of the radical. This discrepancy will be discussed later.

**TABLE 4**
**Dipole Moment Values[a] of the *toward* and *away* Conformations of the Antioxidants Studied, of the *p*-Coumaric and Sinapinic Acids as well as of Their Respective Radicals**

| Antioxidant | *away*[a] | *toward* | Radicals |
|---|---|---|---|
| **I** | 0.76 | 2.52 | 2.58[b]<br>5.24[c]<br>5.13[d] |
| **II** | 2.51 | 4.50 | 1.49[b]<br>4.11[c]<br>3.22[d] |
| **III** | 1.10 | 2.74 | 6.24 |
| **IV** | 0.89 | 2.66 | 5.37 |
| **V** | 1.18 | 2.95 | 5.69 |
| **VI** | 2.67 | 4.26 | 3.85 |
| **X**[e] | — | 3.81[f] | 2.98[f] |
| **XI**[e] | — | 4.99[f] | 1.94[f] |

[a] Dipole moment values in Debye (D).
[b] Dipole moment value of the **VII** radical.
[c] Dipole moment value of the **VIII** radical.
[d] Dipole moment value of the **IX** radical.
[e] *p*-Coumaric acid (**X**) and sinapinic acid (**XI**) do not exhibit *away* conformations.
[f] The dipole moment values of *p*-coumaric and sinapinic acids have been calculated by us and are given for the first time.

The numbers in Table 4 can be divided into two groups. Antioxidants **I** and **II–V** belong to the low-polarity one, whereas **II** and **VI**, presenting at least double the *away* and *toward* dipole moment values compared to the former, belong to the high-polarity group. As stated, the more probable structure of an antioxidant in solution is the *away* conformation; *toward* is the more probable one in the gas phase and/or in very dilute solutions. The same conclusion is drawn on the basis of the total electronic energies of the compounds, because in the gas phase, all *away* conformations appear less energetically stable than the *toward* ones. This could mean that, in dense solutions, any of the **I** and **III–V** antioxidants should adopt the *away* conformation. However, in very dilute solutions the *away* conformation could be converted to the *toward* one. In effect, this leads to an increase in the dipole moment value of an antioxidant, further facilitating its dilution in a polar solvent. This dilution becomes more complete upon radical formation, presenting a higher dipole moment value than its respective *toward* parent conformation, further increasing the concentration of the radical in the polar solvent, and possibly its efficiency. Consequently, a low-polarity antioxidant is expected to be more efficient in higher-polarity solvents than in lower-polarity ones. For a complete study of the more polar compounds, the dipole moment values of **X** (*p*-coumaric acid) and **XI** (sinapinic acid) were considered (8). Inspection of the dipole moment values of **II**, **VI**, **X**, and **XI** shows that, like the low-polarity molecules, their *toward* conformations exhibit higher dipole moment values than the *away* ones (where data are available). However, their radicals exhibit lower dipole moment values than those of the *toward* conformations; in some instances they are smaller by one order of magnitude or more. Consequently, a higher-polarity antioxidant should be more efficient in lower-polarity solvents than in high-polarity ones. Based on the dipole-moment value antioxidant-activity relationship, derived for the lower- and higher-polarity antioxidants under study, the so-called polar paradox (19) could be explained theoretically. Certainly, more evidence is needed to substantiate this finding, mainly because the two groups of compounds in the present study are structurally similar and do not differ widely in polarity.

It was shown before (9) that, on the basis of a bulk oil experiment, **I** is a better antioxidant than **II**. However, theoretical results show that (i) **II** exhibits more polar parent molecules than **I**, and (ii) the opposite holds true for the corresponding radicals of the two compounds. This latter could account for the bulk-oil experimental data of the same compounds and the operation of the radical mechanism for the hydrogen abstraction in the same experiment.

In the case of the monophenols, isoeugenol was found more efficient, in bulk oil, than its two *analogs,* **IV** and **V**. Calculated dipole moment values for the parent compounds did not support this finding unless the corresponding values of the respective radicals were also considered. Thus, if the substituents in the aromatic ring of the antioxidants are not identical, the dipole moment value is not a decisive molecular descriptor for antioxidant activity in such systems. That was also the case with the compounds studied in our previous paper (8), in which the dipole moment value-based antioxidant-activity trend was as follows: ferulic acid > *p*-coumaric acid > sinapinic acid > caffeic acid. However, the experimental trend of the same compounds on the basis of ΔHOF values was caffeic acid > sinapinic acid > ferulic acid > *p*-coumaric acid. Moreover, dipole moment value differences did not explain the performance of the antioxidants studied in dispersed systems (lecithin liposomes and o/w emulsions). For these reasons, two more molecular descriptors, the HOMO eigenvalues and the spin density values, were also considered.

*HOMO eigenvalues.* HOMO eigenvalues are parameters representing molecular electron-donating ability. Redox potential is expected to be directly related to the antioxidant activity; the lower the HOMO eigenvalue, the lower the antioxidant activity of a molecule. The computed HOMO eigenvalues of the *toward* configurations of **I** and **II** are −0.2239 and −0.2294 a.u., respectively. Although these values agree with the experimental findings of the ferric reducing antioxidant power experiment (9), they contradict the Folin–Ciocalteu values. Moreover, the corresponding eigenvalues for **III–V**, being −0.2010, −0.2132, and −0.2102 a.u., respectively, contradict the experimental findings of both previous assays. Hence, although the corresponding experimental antioxidant-activity trends derived from the previous experiments are not identical, theoretical results show that the HOMO eigenvalues of the five (**I–V**) antioxidants are not suitable to predict antioxidant activity. Zhang (5) reached a similar conclusion, as did we (8).

*Spin density values.* The computed spin density values of the atoms constituting the radicals of the antioxidants studied are given in Figure 1. In the radicals **IV-r**, **V-r**, **VII**, **VIII**, and **IX**, almost all spin remains in the benzene ring and its substituents. In contrast, it spreads over all atoms participating in the extended conjugation system in the radicals of **II** (8) and **III**. Hence, the spin delocalization is large in the radicals of **II** and **III** and limited in the radicals **IV-r**, **V-r**, **VII**, **VIII**, and **IX**. The planarity of the radicals of **II** and **III** leads to their full conjugation and to extended spin delocalization. Delocalization in the radicals of **II** and **III** could account for their potential radical-scavenging activity and the superior antioxidant activity of **II** and **III** as compared to those of **IV** and **V**. Furthermore, the lower antioxidant activity of **I**, as compared to that of **II**, could be due to both its higher calculated ΔHOF value and its lower possibility of delocalization. It is well known that a high calculated ΔHOF value means a harder tendency for hydrogen atom abstraction, i.e., difficulty in breaking the phenolic O–H bond. The absence of a high amount of localized spin in the antioxidants studied may diminish the possibility that they will initiate a radical chain reaction (2). However, the relatively high spin values calculated at the *ortho* position of the dihydroeugenol radical could explain its ability to scavenge two moles of DPPH$^\bullet$ per molecule of antioxidant [Table 1 (9)]. In effect, this could lead to a dimerization of two radicals, followed by a regeneration of the two hydroxyl groups (7,20).

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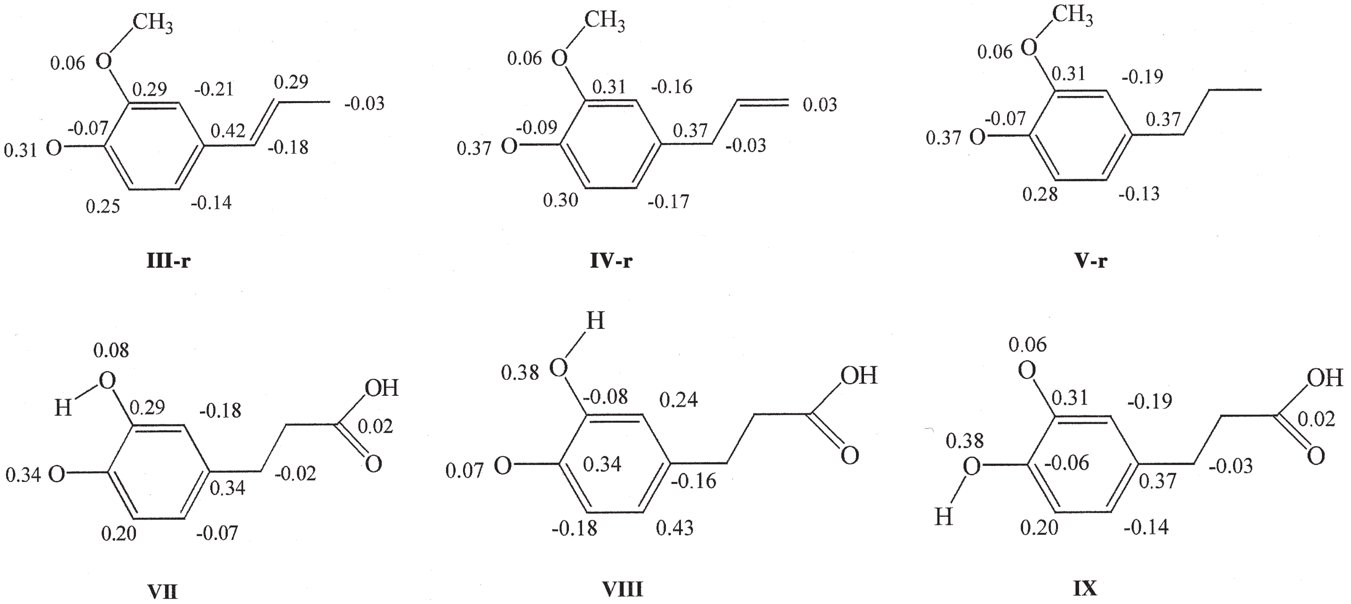

**FIG. 1.** Computed spin density values of the atoms constituting the radicals of the antioxidants studied. Only values ≥0.01 are shown; the benzene ring and the olefinic hydrogens, possessing 0.01 spin values, are omitted for clarity. **III-r**, isoeugenol radical; **IV-r**, eugenol radical; **V-r**, dihydroeugenol radical; **VII**, dihydrocaffeic acid H-bonded radical; **VIII**, dihydrocaffeic acid non-H-bonded radical; **IX**, dihydrocaffeic acid opposite radical.

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