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Donor-acceptor interactions as descriptors of the free radical scavenging ability of flavans and catechin

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ABSTRACT

Interest in food phenolics has increased in recent years largely due to their antioxidant capacity, free radical scavenging, and potential health benefits. In literature two main reaction mechanisms have been proposed for their role as free radical (FR) scavengers, i.e., the mechanism of a hydrogen atom transfer (HAT) governed by the O—H bond dissociation enthalpy (BDE), and the mechanism of single electron transfer (SET) governed by an electron transfer process, the ionization potential (IP) playing an important role.

Thirty nonplanar structures were analyzed. The study of (+)-catechin (CTQ) and (4α → 6″, 2α → *O* → 1″)-phenylflavans with a R′ = H, R = OH; R′ = OH, R = H, and R′ = OH, R = OH substitution is performed herein. Catechol, phenol, and resorcinol are also included as references. Results obtained with B3LYP hybrid functional with 6-311++G(d,p) and 6-31G(d,p) basis set are analyzed. Two new indicators arising from electron delocalizations are presented herein, thus showing that there is a different set of donor-acceptor interactions to explain FR scavenging mechanisms.

1. Introduction

Interest in food phenolics has increased in recent years largely due to their antioxidant capacity, free radical scavenging, and potential health benefits. Search for natural antioxidants for use in food or drugs is increasing to replace synthetics, some of them reported as carcinogenics [1].

Antioxidants are an important class of compounds that scavenge free radicals (FR), which arise as intermediates of oxidation reactions. Oxidative stress has been implicated in the development of neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington diseases, epileptic seizures, aging, in addition to promoting certain cancers [2–4].

The antioxidant efficiency of flavonoids has been related to the number of hydroxy groups in the molecule, conjugation, and resonance effects, as well as a hydrogen donor ability to reduce FR effects [5]. Moreover, the effectiveness of some flavonoids to inhibit FR depends on the structure (conformation), thermochemical properties, and also concentration and reaction rates (kinetic properties) [6].

Computational chemistry is one of the most powerful tools to make progress in this field, and several studies on this subject are reported in the literature [7–13]. Valuable information is provided lowering costs and time involved in experimental or clinical studies, and also inferring about the effects of different molecular characteristics on the properties of the flavonoids. Theoretical data may be used as a valid tool to predict the structure-activity relationships (SAR) of a compound and also for designing new potential antioxidants. The comparison of the theoretical and experimental data supports modern theoretical approaches able not only to explain controversial experimental facts but also to predict the chemical behavior and antioxidant activity of novel compounds [14].

In literature two main reaction mechanisms have been proposed, by which phenolic antioxidants can perform their role as FR scavengers, i.e., the mechanism of a hydrogen atom transfer (HAT), and the mechanism of single electron transfer (SET) [15–33]. Also recently an alternative mechanism including a complex formation has been demonstrated for glycerol and other polyols [34].

Both HAT and SET mechanisms of FR scavenging can be modeled by computational chemistry. HAT mechanism is governed by the O—H bond dissociation enthalpy (BDE), which is a molecular property used for assessing FR scavenger potential of a molecule. This is calculated as the difference between the formation heat of the molecule and its radicals, which accounts for the O—H bond breakage energy. The SET mechanism is governed by an electron transfer process, playing important roles both the ionization potential (IP) and $R'OH^{+\bullet}$ radical cation (RC) reactivity.

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According to Wright et al. [29] to design an optimal synthetic antioxidant, i.e., for a given biological role, first BDE and IP must be known. This information will be also useful to elucidate SAR for natural antioxidants, such as catechol-containing flavonoids.

BDE thermochemical calculations are very useful for the characterization of the antioxidant activity of a large group of antioxidants [29,35], and can reproduce experimental values with good accuracy.

The reliability of the methods based on the Density Functional Theory (DFT) to predict the main antioxidant properties and reaction mechanisms involved in radical scavenging reactions of food chemicals is accepted in the community [17].

Currently is advanced in the determination of thermodynamic parameters, and other useful descriptors for analyzing the antioxidant action [36]. However, yet very few reports attempt to explain or rationalize such descriptor values and trends with *ab initio* calculations.

We have previously reported the analysis of the stereoelectronic effects induced by R = H, OH and OCH_3 substitution in *Z*-isomers of (4α → 6″, 2α → *O* → 1″)-phenylflavans [37]. In a more recent work, the study of (4α → 6″, 2α → *O* → 1″)-phenylflavans substituted with R′ = OH, R = OH showed the occurrence of cooperatively-acting charge delocalization mechanisms that define "delocalization routes", thus giving rise to interactions between different rings of the compound, even when not sharing the same plane [38]. The findings of both reports highlighted the key role played by hyperconjugative interactions in the stereoelectronic effects induced by substitution as a relevant factor for understanding the associated BDEs and IPs values.

The aim of this paper is to investigate the conformational and electronic properties of different flavonoids substituted with OH groups. These compounds were chosen to evaluate catechol and resorcinol effects on the antioxidant capacity of nonplanar flavonoids.

The effects of the basis quality on the calculation of the parameters of interest and description of the systems are also discussed. Minimal computational costs are necessary for the inclusion of different solvent effects, and for analyzing the reaction kinetics of interest for studies of other naturally-occurring antioxidants.

Accordingly, the study of (+)-catechin (CTQ) and (4α → 6″, 2α → *O* → 1″)-phenylflavans with R′ = H, R = OH (FFR′HROH); R′ = OH, R = H (FFR′OHRH), and R′ = OH, R = OH (FFR′ROH) substitution is performed herein. The selection has a methodological reason looking for a stepwise study with an increasing level of structural complexity. Catechol, phenol, and resorcinol are also included [39–41]. Phenol BDE is a reference value for all phenolic antioxidants. Its computational calculation is also a quality marker for theoretical results; the present calculation values are within experimental error, which validates the schemes followed.

Results according to three calculation schemes using density functionals and two different basis sets are studied. Electronic charge delocalizations that explain the thermodynamic parameter values associated with SET and HAT mechanisms are analyzed.

Descriptors to predict which structure of the parent molecule fit the best qualities as an antioxidant relative to BDE and IP values are searched. Electron delocalization routes and structural characteristics leading to the best BDE and IP values are defined.

The whole analysis is carried out taking into account our previous reports [37,42,43], thus studying the role of the substituents of both resorcinol and catechol rings in the initial description of the antioxidant capacity of this kind of compounds. This description is based on the study of electron distribution, and the corresponding electron delocalization effects. This paper deepens in this analysis with the hypothesis that there are different electron delocalization mechanisms to explain each proposed reaction.

The study of the in vacuum ("zero order") intrinsic characteristics of these compounds is relevant to measure the effects of different solvents in subsequent studies, and to contribute to modeling the effect of both polar and non-polar solvents on the antioxidant activity.

2. Methods

Calculations were carried out with the Gaussian 03 software package [44]. Geometries of the parent molecules were optimized by the Density Functional Theory using the B3LYP hybrid functional [45,46]. The suitability of this functional for studies of bond dissociation enthalpy involving natural isoflavonoids has already been reported elsewhere [11,17,20,23,47]. Two basis sets were used, i.e., 6-31G(d,p) (type of calculation hereinafter referred to as DZ), and 6-311++G(d,p) (type of calculation hereinafter referred to as TZ). At these same levels (DZ and TZ) zero point vibrational energy (ZPE) and enthalpy thermal contribution (ETC) were calculated, and AIM (atoms in molecules) and natural bond orbitals (NBO) analyses were performed.

Based on optimized geometries, ZPE and ETC corrections obtained with the 6-31G(d,p) basis set, set single-point calculations with the 6-311++G(d,p) basis set, and a further AIM/NBO analysis were carried out, which is the calculation scheme hereinafter called MIX. Restricted and unrestricted calculations were carried out for closed- and open-shell systems, respectively.

Both HAT and SET mechanisms were analyzed. In the HAT mechanism, the hydrogen atom transfer of the O—H bond is studied. The O—H bond dissociation energy (BDE) is associated with HAT mechanism, and is computed by the enthalpy (H) difference between the products and reactants of the reaction:

where $H(R'O^{\bullet})$ is the enthalpy of the radical generated by H abstraction; $H(H^{\bullet})$ is the hydrogen atom enthalpy (−0.499897 Hartree at this level of theory); and H(R′OH) is the parent molecule enthalpy. BDE is an important theoretical descriptor that characterizes the radical scavenging activity of antioxidants.

The SET mechanism can occur in parallel to HAT. In this mechanism the antioxidant donates an electron to FR, turning itself in a CR. IP is associated with the SET mechanism, and is computed by the electronic energy difference of the reactants and products. The lower the IP value, the easier is the electron abstraction. IP values were determined as follows:

$$IP = Erc - Ep$$

where Ep and Erc indicate the electronic energy of the parent molecule, and that of the RC generated.

The calculated IP accounts for adiabatic IP, whereby the RC structure is fully optimized. At B3LYP/6-311++G(d,p) level the vibrational analysis for both parent molecules and radicals reaction products is performed. The values obtained are used to verify that the structures studied account for energy minima, and also to correct energy values by considering ZPE and ETC (which includes vibrational contributions and ZPE).

No spin contamination is found in the radicals, the $\langle S^2 \rangle$ values being not greater than 0.750 in all cases. Phenol, catechol, and resorcinol as reference compounds are studied by the same methodology

and calculation level, so that the present values can be also compared with those of other antioxidants in the literature.

Topological analysis was performed with the PROAIM software [48] at the three calculation levels proposed. The most significant local topological properties in bond critical points (BCPs) of the chemical bonds are characterized. This paper mainly analyzes the ellipticity ε, defined as λ_1/λ_2-1. The similarity between perpendicular curvatures (λ_1 and λ_2) at BCP is measured by the ellipticity, and quantifies the extent to which density is preferentially accumulated in a given plane containing the bond. When the bond is cylindrically symmetric, ε = 0 because $\lambda_1 = \lambda_2$, e.g., a C—C single bond in ethane, and a triple bond in acetylene. The ε values can be useful as a measure of the bond π character.

The NBO analysis is performed with NBO version 3.1 software [49] implemented in the Gaussian 03 package, which allows describing electron charge delocalizations typical of the structures under study through a donor-acceptor picture of hyperconjugative interactions. For each NBO donor (*i*), and each NBO acceptor (*j*), the second-order perturbation energy ($E^{(2)}$) associated with *i*/*j* delocalization was as follows,

$$E^{(2)} = -n_i \frac{F_{ij}^2}{\varepsilon_j - \varepsilon_i}$$

where n_i is the occupation or population of the donor orbital *i*; ε_i and ε_j are the orbital energies involved in the interaction, and $F_{i,j}$ is the element *i*, *j* of the Fock or Kohn–Sham operator matrix.

3. Results and discussion

From the study of the conformational space of (4α → 6″, 2α → *O* → 1″)-phenylflavan substituted with R′ = H, R = OH; R′ = OH, R = H; R′ = R = OH; and (+)-catechin, the most stable conformers were selected according to previous reports [37,38,42,43] (FFR′HROH$_{CT}$, FFR′OHRH$_{CTa}$, FFR′OHRH$_{CTb}$, FFR′ROH$_{CTa}$, FFR′ROH$_{CTb}$ and CTQ$_{CTa}$ CTQ$_{CTb}$, according to nomenclature above defined) as shown in Fig. 1. A total of 30 molecules were studied including the structures of radicals and radical cations from modeling the reactions of interest (Eqs. (1) and (2)).

(1)

(2)

The knowledge of structural and electronic characteristics is essential for elucidating the FR scavenging capacity of polyphenolics. Systems with multiple OH groups can lead to several radical species depending on the group that is radicalized. By abstracting hydrogen atoms of various OH groups of the molecules (see Eq. (1)), it is possible to obtain different radical species, which are called R1 and R2 in abbreviated form (Fig. 2) (OH belonging to catechol ring), R3 and R4 (OH belonging to resorcinol ring).

BDE values obtained in gas-phase with the different types of calculation (DZ, TZ, and MIX), and the experimental values from literature are shown in Table 1.

The calculated BDE of phenol is often found in literature as reference value, usually up to 5 kcal·mol^{-1} lower than the experimental value (on average 88.7 kcal·mol^{-1}) [17].

As shown in Table 1, the BDE value of phenol by MIX calculation is 82.71 kcal·mol^{-1} (81.43 kcal·mol^{-1} and 82.80 kcal·mol^{-1} by DZ and TZ calculations, respectively). According to other authors [11,50–53] the calculated BDE values (B3LYP/6-311++G(d,p), B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p), B3LYP/6-31G(d,p), and B3LYP/6-311++G(3df, 3pd) levels) of phenol fall in the range of 82–84 kcal·mol^{-1}, which is consistent with both the TZ and MIX calculations, and experimental values.

As mentioned above, the O—H bond dissociation enthalpy (BDE) is an important parameter to evaluate the antioxidant action; the lower the BDE value, easier will be the reaction of FR quenching. BDE decrease means that the reaction will be more favorable due to the greater ease of H donation. In the species studied this condition occurs when the radical is obtained by abstracting hydrogen of the OH group that is not involved in the intramolecular hydrogen bridge interaction of the catechol portion (leading to radical R1). In fact, BDE values corresponding to R1 are between 4 and 9 kcal·mol^{-1} lower than those of the other radical species (R2, R3, and R4) as shown in Table 1.

BDE values of b-type structures for R1 are lower than for a-type, showing the following order: FF < catechol < CTQ < phenol. Instead, BDE values for R3 generally show the following order: CTQ < FFR′OHRH < FFR′ROH < resorcinol < phenol. CTQ and resorcinol show greater BDE values for R4 than for R3, while FF behaves inversely. For R4 a trend similar to that of R1 is observed: FF < CTQ < resorcinol < phenol.

Although various species trends are similar by different types of calculations, the values of such thermodynamic parameters are underestimated up to 3.4% by DZ calculation compared to TZ. The values calculated by MIX roughly follow the same trend as by TZ, showing slight deviations (sometimes increases, and other decreases) not exceeding 1.4%. Some TZ trends between A-type and B-type conformers of the same species are not reproduced by MIX and DZ schemes.

Taking into account our previous reports [37,38,42,43], it is now deepened in the search and characterization of the relevant electronic delocalizations. Therefore, it is important to study in the parent molecule hyperconjugative interactions involving the $\sigma_{O—H}$ natural orbital that will undergo homolytic break in each case studied (R1-R4). The values of $E^{(2)}$ second order stabilization energy by TZ calculation for $\sigma_{O—H} \rightarrow \sigma^*_{C—C}$ transfer (hereinafter, *O—H donor role*), and BDE values are shown in Table 2. It is observed that as the donor role increases, the BDE value also grows.

This dependence is analyzed in Fig. 3(i) according to the three calculation schemes (TZ, MIX and DZ), and there is a linear relationship as shown by the correlation coefficient R^2 of 0.98 with TZ calculation. DZ scheme fits worse, MIX being acceptable for its proximity to TZ fit. This result is of interest to apply this kind of analysis in larger systems, and in reaction kinetics calculations involving solvent effects.

From the study of electron delocalization effects in vacuum by NBO analysis, then the lower the O—H donor role of a structure, the lower is the BDE value. Therefore, the OH group is "less committed" with the rest of the structure, thus the hydrogen atom being more available to interact with FR.

The decrease in the donor role of the O—H bond ($\sigma_{O—H} \rightarrow \sigma^*_{C—C}$) can be analyzed in Fig. 3(ii). Therefore, the donor role decreases when the overlap between the $\sigma_{O—H}$ orbital and the $\sigma^*_{C—C}$ orbital of the aromatic ring ($F_{i,j}$) decreases. The relationship shows a linear fit with a coefficient R^2 of 0.98. Again a loss of quality is realized in DZ scheme description, and MIX applicability if required by the system dimension. The question now is: what is the dominant factor in defining this overlap? The hybridization of the NBOs involved

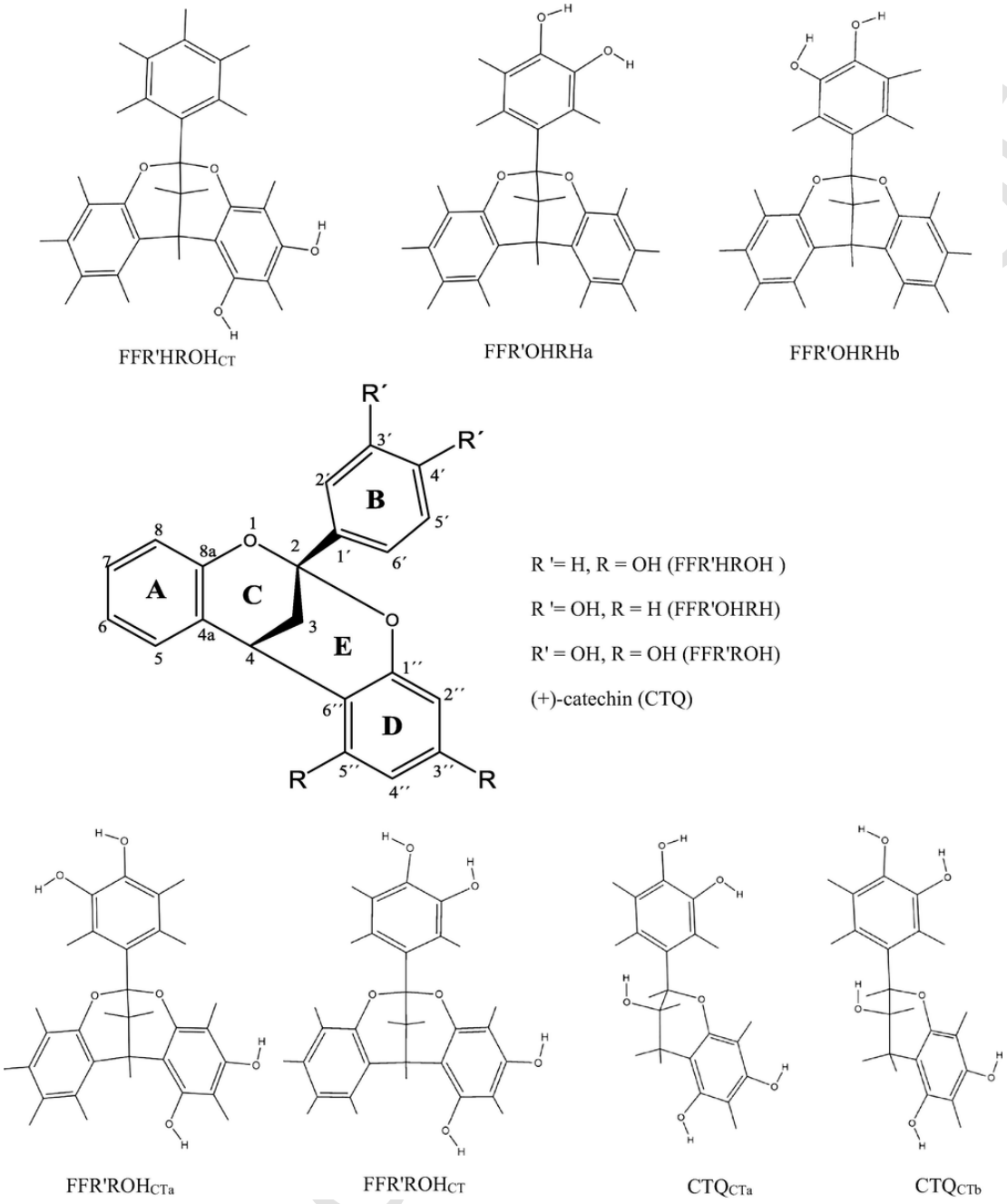

Fig. 1. Structures of (4α → 6″, 2α → *O* → 1″)-phenylflavan substituted with R′ = OH, R = H (FFR′OHRH), R′ = R = OH (FFR′ROH$_{CT}$), R′ = H, R = OH (FFR′HROH$_{CT}$), and (+)-catechin (CTQ$_{CT}$).

is then analyzed, and the *s*-type contribution of the substituted carbon atom to the acceptor bonding orbital ($\sigma^*_{C—C}$) is found as a key fact. Indeed, Fig. 3(iii) shows that the better the BDE, the smaller is the substituted carbon contribution to C—C bond *s* character ($\sigma^*_{C—C}$ hybridization). Therefore, electron charge delocalization that it is important in describing BDE values will decrease with "s" contribution decreasing of the carbon bonded to OH (substituted carbon), which will donate its H atom by HAT mechanism, to the hybridization of the natural bonding orbital $\sigma^*_{C—C}$ (acceptor).

Furthermore, according to other authors [54], the analysis of *para*- and *meta*-substituted phenols showed that there is a good correlation between BDE values and *C—O bond length* of the OH group that will donate its H atom by HAT mechanism (the longer the C—O bond, the lower is the BDE of the O—H bond). We corroborated this relationship in flavans at TZ calculation level, and found that indeed the best BDE values accounted for higher length values of the various C—O bonds (Fig. 3(iv)).

Therefore, the *O—H bond donor role* and the *C—O bond length* are useful descriptors to predict BDE values, finding a better fit for the proposed indicator in this paper (correlation coefficient 0.99 *versus* 0.95 for *O—H donor role* and *C—O bond length*, respectively).

This would indicate that both the *C—O bond length* and the *O—H donor role* can serve to design new phenolic antioxidants as an initial criterion in the search for compounds with better FR scavenging

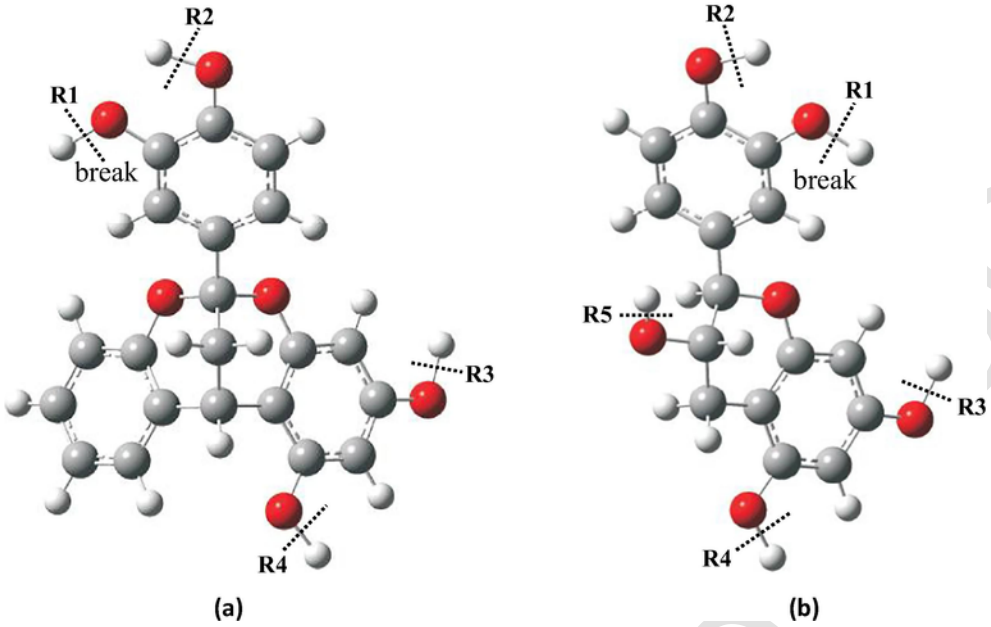

Fig. 2. Radical species resulting after H atom abstraction from the hydroxy groups by HAT mechanism. Only species resulting from FFR′ROH$_{CTa}$, and CTQ$_{CTa}$, and possible O—H bond homolytic cleavage points by HAT mechanism giving rise to distinct radical species (R) are shown in the scheme.

Table 1
BDE values in gas phase calculated by different calculation schemes (B3LYP/6-311++G(d,p), TZ, B3LYP/6-31G(d,p)/6-311++G(d,p), MIX, and B3LYP/6-31G(d,p), DZ). Values are expressed in kcal·mol^{-1}.

Calculation scheme	Radical species	FFR′ROH$_{CTb}$	FFR′ROH$_{CTa}$	FFR′HROH$_{CT}$	FFR′OHRH$_b$	FFR′OHRH$_a$	CTQ$_{CTa}$	CTQ$_{CTb}$	Catechol	Resorcinol	Phenol
B3LYP/6-311++G**	R1	73.86	74.37		73.93	74.34	75.07	74.1	73.94		
	R2	82.74	82.67		82.88	83.88	82.88	83.59	82.72		
	R3	81.89	81.98	81.86			81.34	81.38		82.42	
	R4	81.1	81.24	81.26			81.77	81.53		83.72	
	R5										82.8
B3LYP/6-31G**/6-311++G**	R1	73.98	74.4		74.00	74.37	75.11	74.1	74.05		
	R2	82.79	82.66		82.88	82.73	82.87	83.56	82.79		
	R3	81.85	81.9	81.79			81.29	81.32		82.29	
	R4	81.14	81.24	81.27			81.78	81.51		83.65	
	R5										82.71
B3LYP/6-31G**	R1	71.54	71.9		71.65	72.1	72.66	71.56	71.43		
	R2	81.15	80.94		81.32	81.25	81.16	81.87	81.01		
	R3	80.82	80.7	80.81			80.31	80.41		81.1	
	R4	79.86	79.79	80.02			80.65	80.39		82.45	
	R5										81.43
Experimental							77.9[h, i]		81.8[a]	88.21[c]	88.68[d]
									81.2[b]	90.8, i	82.89[e]
									81.9[h, i]		88.3 (± 0.8)[f]
											87.0 (± 1)[g]

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ability. It is interesting to point out that both the C—O bond length and O—H donor role determinations require geometry optimization of the parent molecule only, while BDE calculation requires geometry optimization and energy calculations for both the molecule and its radical, reinforcing the value of the displayed results.

Analyzing now the effects of the calculation type used, the correlation coefficients for linear fit (R^2) corresponding to the BDE rela-

Table 2
The "*O—H bond donor role*" descriptor. Values of indicators that allow predicting from the parent molecule the antioxidant capacity of the compounds by HAT mechanism, obtained by the B3LYP/6-311++G(d,p), TZ calculation scheme in gas phase.

Radical Species	Structure	Donor role[a]	Fij[b]	C-O length[c]	*s* Character[d]
R1	CTQ_{CTa}	3.86	0.063	1.377	35.35
	CTQ_{CTb}	3.82	0.062	1.377	34.17
	$FFR'ROH_{CTa}$	3.86	0.063	1.379	35.48
	$FFR'ROH_{CTb}$	3.84	0.063	1.378	35.44
	Catechol	3.81	0.062	1.379	35.50
	$FFR'OHRH_a$	3.85	0.063	1.379	35.49
R2	CTQ_{CTa}	5.35	0.074	1.362	38.68
	CTQ_{CTb}	5.43	0.074	1.363	38.78
	$FFR'ROH_{CTa}$	5.35	0.074	1.363	38.63
	$FFR'ROH_{CTb}$	5.07	0.072	1.364	38.76
	Catechol	5.32	0.073	1.364	38.69
	$FFR'OHRH_a$	5.35	0.074	1.363	38.62
R3	CTQ_{CTa}	4.98	0.071	1.369	36.87
	CTQ_{CTb}	4.98	0.071	1.37	36.87
	$FFR'ROH_{CTa}$	4.99	0.071	1.368	36.89
	$FFR'ROH_{CTb}$	4.99	0.071	1.369	36.89
	$FFR'HROH_{CT}$	4.98	0.071	1.369	36.9
	Resorcinol	4.95	0.071	1.369	36.77
R5	Phenol	4.96	0.071	1.370	37.19

[a] Values expressed in kcal·mol^{-1}.

[b] Values expressed in a.u.

[c] C—O bond length of the OH group that will donate its H atom by HAT. Values expressed in Å.

[d] s-type contribution of the substituted carbon atom to the acceptor bonding orbital ($\sigma^*_{C\text{-}C}$). Values expressed in %.

tionships, donor roles, orbital overlap, and *s*-type contribution to natural orbitals also show that the MIX-type calculation leads to very close results to those of TZ calculation. Since our subsequent interest is the study of larger compounds to approach the analysis of other naturally-occurring flavonoids, these results validate the use of MIX for the molecular basis study of BDE trends by description of electronic delocalizations in the parent molecule. This is of great interest to continue modeling the reactions and their kinetics in solution as would minimize computational costs.

The IP values calculated in gas phase (Table 3) show in general the following order for the compounds: FFR′ROH < FFR′HROH < FFR′OHRH < CTQ < catechol < resorcinol < phenol for all types of calculations. Once again values are underestimated up to 5.6% for DZ calculation compared to TZ. The values for MIX roughly follow the same trend as for TZ (sometimes increases, and other decreases) showing a greater difference not exceeding 2.7% for IP values of FFR′OHRH.

The observed IP differences for MIX scheme compared to TZ calculation are greater than the BDE differences. These results show that it is advisable to calculate this marker at TZ level especially if IP differences are small.

Selected donor-acceptor interactions and second order stabilization energies $E^{(2)}$ from NBO study calculated at B3YP/6-311++G(d,p) level of theory are shown in Table 4. No "b"-type structures are shown since the behavior is similar (see Supplementary Material). The sum of energies of the selected interactions correlates with the IP value obtained for each molecule, and describes charge delocalization effects, which become more effective as the IP improves (decreases). Fig. 4 outlines the tabulated delocalizations, and shows that the selected charge transfers (Table 4) are concatenated indicating electron charge delocalization routes for modeling the interaction of π-electron system of resorcinol/catechol ring with the rest of the structure in gas phase. Fig. 5 shows the relationship, at TZ level, between IP values and charge transfers discussed for all structures chosen for this study (correlation coefficient $R^2 = -0.99$ for linear fit).

Based on Table 4 and Fig. 5, it is concluded that the more effective (greater sum) the defined electron charge delocalization routes, the lower is the IP value. Selected delocalizations are presented as a new descriptor of interest to rationalize IP values, which we propose to call "*π → σ delocalization route*". It is worth mentioning that the descriptor thus defined only takes into account information of the electronic distribution behavior of the parent system.

Our previous results showed that in *Z*-isomers of (4α → 6″, 2α → *O* → 1″)-phenylflavans substituted with R = H, OH and OCH_3, electron donation mainly affected ring D, thus indicating the relevance of electron delocalization from substituents to ring D in the energy stabilization of the parent perturbed structure (RC) in the SET mechanism. In addition, according to SET, one electron would be removed from the highest occupied orbital (HOMO) of the parent molecule to give RC. Therefore, it appears important to consider both the substituted ring(s) and HOMO distribution.

The HOMO for each of the studied parent structures, and mean ellipticity (ε) of each ring are shown in Fig. 4. In each instance a more reactive ring occurs, which matches regions where HOMO localization is higher. The LP delocalization chosen in the "*π → σ delocalization route*" descriptor (Table 4) is for populating the region where HOMO shows the highest concentration: $C_{4''}—C_{3''}$ bond area ($\pi^*_{C4''—C3''}$ natural orbital) for FFR′ROH, FFR′HROH, and CTQ, or $C_{2'}—C_{3'}$ and $C_{4'}—C_{5'}$ bonds area ($\pi^*_{C2'—C3'}$ and $\pi^*_{C4'—C5'}$ natural orbitals) for $FFR'OHRH_a$ and $FFR'OHRH_b$, respectively). The ring selected as the most reactive, and relevant in rationalizing IP trends (according to Table 4 and Fig. 5) also has the highest average ellipticity within each compound (Fig. 4). This indicates by AIM analysis a higher π-electron availability, from which selected charge delocalizations set out. In this regard it is important to highlight the role played by $2n_{O3''} \rightarrow \pi_{C4''—C3''}$ transfer ($2n_{O4'} \rightarrow \pi_{C2'—C3'}$ and $2n_{O4'} \rightarrow \pi_{C4'–C5''}$ in $FFR'OHRH_a$ and $FFR'OHRH_b$, respectively; named "1"-type chain linkage) to provide electron population to π-electron system of the reactive ring ("2"-type chain linkages). It is then concluded that another key transfer is that having as donor the $\pi_{C5''—C6''}$ bonding orbital of the resorcinol ring (or $\pi_{C1'—C6'}$ of catechol in FFR′OHRH), which delocalizes on a σ-symmetry antibonding orbital, and thus connects such ring system with σ-system of the other rings by the so-called "negative hyperconjugative interaction" ("3"-type chain linkage). That is, a π bonding orbital of the resorcinol-type ring (D-ring in FF or A-ring in CTQ) or catechol ring (in FFR′OHRH) is involved in charge delocalization routes that bring the π-electron system of such rings in communication with the σ-electron system of the remaining ring system.

The proposed descriptor then provides the possibility to analyze the reaction of donating an electron in two stages. A first stage ("1"- and "2"-types chain linkages), where it is important to have a π-enriched ring, from which FR will take an electron; in this stage is then significant the presence of substituents that increase electron availability in the π system of such ring. In the second stage, the "*π → σ delocalization route*" descriptor shows that it is also important to have a good delocalization of the own π-electron distribution. These latest findings indicate that although π-electron availability is necessary it is also very important to quickly attenuate destabilizing effects from the electron loss donated to FR. Our analysis leads to the possibility to analyze separately this second stage of the reaction, in which system possibilities to stabilize its electron distribution are very important after the antioxidant disturbance due to interacting with FR; this stabilization further depends on the possible σ-electron system delocalization ("4"-type chain linkages).

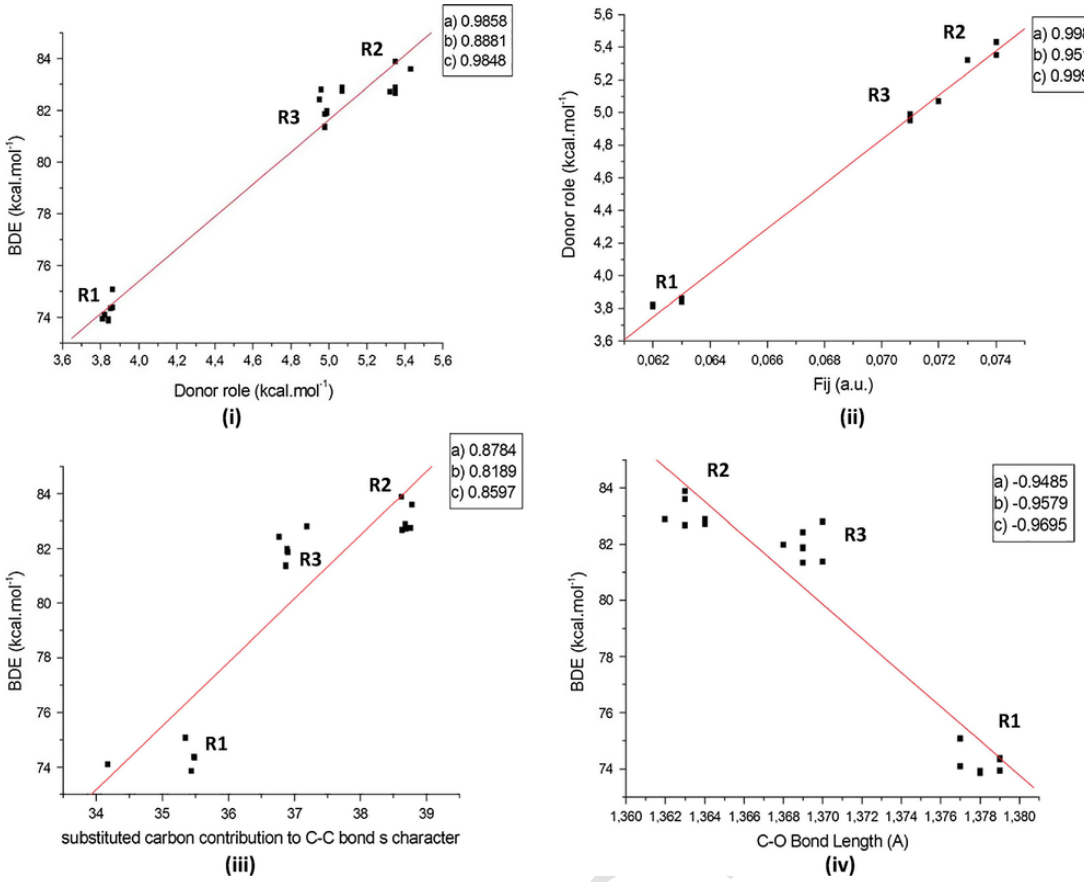

Fig. 3. BDE values obtained by TZ calculation scheme, $E^{(2)}$ second order stabilization energy values for the $\sigma_{O\text{-}H} \rightarrow \sigma^*_{C\text{-}C}$ transfer ("*O—H donor role*" descriptor) (i), overlap between $\sigma_{O\text{–}H}$ and $\sigma^*_{C\text{–}C}$ orbitals of the aromatic ring ($F_{i,j}$) (ii), substituted carbon atom "*s*"-contribution to the $\sigma^*_{C\text{-}C}$ natural bonding orbital hybridization (acceptor) (iii), and *C—O bond length* associated with the OH group that will donate its H atom (iv). Correlation coefficient R^2 for linear fit according to TZ calculation scheme (a), DZ calculation scheme (b), and MIX calculation scheme (c).

Table 3
Values obtained in gas phase by different calculation schemes (B3LYP/6-311++G(d,p), TZ, B3LYP/6-31 G(d,p)/6-311++G(d,p), MIX, and B3LYP/6-31 G(d,p), DZ). Values are expressed in kcal·mol^{-1}.

Calculation scheme	FFR′ROH$_{CTb}$	FFR′ROH$_{CTa}$	FFR′HROH$_{CT}$	FFR′OHRH$_b$	FFR′OHRH$_a$	CTQ$_{CTa}$	CTQ$_{CTb}$	Catechol	Resorcinol	Phenol
B3LYP/6-311++G(d,p)	164.51	165.15	167.04	167.05	167.93	169.36	169.79	183.95	186.39	192.18
B3LYP/6-31 G(d,p)/6-311++G(d,p)	164.58	165.22	166.99	171.62	171.74	170.58	169.51	183.98	186.26	192.09
B3LYP/6-31 G(d,p)	155.93	156.24	159.04	163.07	163.72	161.22	160.19	175.49	178.22	184.85
Experimental values						100.77 [a]		187.94 [b]	199.01[c]	195.78 [e]
								197.4 [c]	199,012[d]	197.40[c]

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Similar electron charge delocalization routes lead to more effectiveness for structures with A + D + C + E + B rings. Besides, the σ-electron system delocalization routes modeling ring interactions are more effective in phenylflavans (these results are in agreement with those recently reported) [38]. It is concluded that the presence of the catechol ring is important for the two proposed mechanisms, and both BDE and IP improve with a higher ring amount in the system (FF with A + D + C + E + B rings *vs*. CTQ with A + C + B rings). Consequently, phenylflavans with R′ = R = OH are expected to be better antioxidants than CTQ.

It is evident for IP that the descriptor implies a delocalization mechanism with global characteristics defining an effect with a strong dependence on the antioxidant structure (definitely "global" or "non-local" descriptor). On the contrary, BDE is described by a local delocalization mechanism (the properties of the O—H bond to be broken or very nearby regions are important; therefore, strongly "local" descriptor) at least in the set of studied structures, which although different species they show strong structural similarity. Therefore, it cannot be ruled out that when applying the "*O—H donor role*" descriptor to structurally very different compounds it may be

Table 4
The "$\pi \rightarrow \sigma$ *delocalization route*" descriptor. Second order stabilization energies $E^{(2)}$ for donor-acceptor interactions defining electron charge delocalization routes for modeling the π-electron system interaction of resorcinol/catechol ring with the rest of the structure in gas phase, and related with IP value, calculated at the B3YP/6-311++G(d,p) level of theory. Values are expressed in kcal·mol^{-1}.

	FFR′ROH$_{CTa}$			FFR′HROH$_{CT}$			FFR′OHRH$_a$			CTQ$_{CTa}$			Catechol			Resorcinol		
Chain linkage type	Donor	Acceptor	$E^{(2)}$	Donor	Acceptor	$E^{(2)}$	Donor	Acceptor	$E^{(2)}$	Donor	Acceptor	$E^{(2)}$	Donor	Acceptor	$E^{(2)}$	Donor	Acceptor	$E^{(2)}$
1	$2n_{O3''}$	$\pi^*_{C3''-C4''}$	27.78	$2n_{O3''}$	$\pi^*_{C3''-C4''}$	27.73	$2n_{O4'}$	$\pi^*_{C4'-C5'}$	27.23	$2n_{O7}$	π^*_{C6-C7}	27.48	$2n_{O4'}$	$\pi^*_{C4'-C5'}$	26.97	$2n_{O3''}$	$\pi^*_{C2''-C3''}$	27.69
							$2n_{O3'}$	$\pi^*_{C2'-C3'}$	23.35	$2n_{O5}$	π^*_{C4a-C5}	26.62						
2	$\pi_{C3''-C4''}$	$\pi^*_{C5''-C6''}$	14.52	$\pi_{C3''-C4''}$	$\pi^*_{C5''-C6''}$	14.51	$\pi_{C4'-C5'}$	$\pi^*_{C1'-C6'}$	20.73	π_{C6-C7}	π^*_{C4a-C5}	14.25	$\pi_{C4'-C5'}$	$\pi^*_{C1'-C6'}$	20.53	$\pi_{C2''-C3''}$	$\pi^*_{C4''-C5''}$	14.36
	$\pi_{C1''-C2''}$	$\pi^*_{C5''-C6''}$	27.39	$\pi_{C1''-C2''}$	$\pi^*_{C5''-C6''}$	27.33	$\pi_{C2'-C3'}$	$\pi^*_{C1'-C6'}$	18.64	π_{C8-C8a}	π^*_{C4a-C5}	27.36	$\pi_{C2'-C3'}$	$\pi^*_{C1'-C6'}$	18.22	$\pi_{C1''-C6''}$	$\pi^*_{C4''-C5''}$	24.52
	$\pi_{C4a-C8a}$	$\pi^*_{C5''-C6''}$	1.06	$\pi_{C4a-C8a}$	$\pi^*_{C5''-C6''}$	1.07												
	π^*_{C5-C6}	$\pi^*_{C4a-C8a}$	21.29	π^*_{C5-C6}	$\pi^*_{C4a-C8a}$	21.34												
	π^*_{C6-C7}	$\pi^*_{C4a-C8a}$	19.31	π^*_{C6-C7}	$\pi^*_{C4a-C8a}$	19.28												
3	$\pi_{C5''-C6''}$	σ^*_{C3-C4}	1.06	$\pi_{C5''-C6''}$	σ^*_{C3-C4}	1.08	$\pi_{C1'-C6'}$	σ^*_{C2-O}	1.75	π_{C4a-C5}	σ^*_{C4-H}	3.43						
4	σ_{C3-C4}	$\sigma^*_{C2-C1'}$	2.84	σ_{C3-C4}	$\sigma^*_{C2-C1'}$	2.84	σ_{C2-O}	$\sigma^*_{C1''-C2''}$	2.28	σ_{C4-H}	σ^*_{C3-H}	3.06						
							$\sigma_{C1''-C2''}$	$\sigma^*_{C3''-H}$	2.45	σ_{C3-H}	σ^*_{C2-H}	2.98						
	$\sigma_{C2-C1'}$	$\sigma^*_{C2'-C3'}$	2.03	$\sigma_{C2-C1'}$	$\sigma^*_{C2'-C3'}$	2.29	σ_{C3-H}	$\sigma^*_{C4-C6''}$	2.63	σ_{C2-H}	$\sigma^*_{C1'-C2'}$	4.66						
	$\sigma_{C2-C1'}$	$\sigma^*_{C5'-C6'}$	2.25	$\sigma_{C2-C1'}$	$\sigma^*_{C5'-C6'}$	2.31	$\sigma^*_{C4-C6''}$	$\sigma^*_{C4''-C5''}$	2.38	$\sigma_{C1'-C2'}$	$\sigma^*_{C6'-H}$	2.76						
										$\sigma_{C6'-H}$	$\sigma^*_{C4'-C5'}$	3.7						
	$\sigma_{C2'-C3'}$	$\sigma^*_{C4'-O4'}$	3.38	$\sigma_{C2'-C3'}$	$\sigma^*_{C4'-H}$	2.61	σ_{C2-O}	σ^*_{C3-H}	1.04	$\sigma_{C4'-C5'}$	$\sigma^*_{C3'-O3'}$	3.37						
	$\sigma_{C5'-C6'}$	$\sigma^*_{C4'-O4'}$	4.44	$\sigma_{C5'-C6'}$	$\sigma^*_{C4'-H}$	2.61	$\sigma_{C4''-C5''}$	$\sigma^*_{C3''-H}$	2.65	$\sigma_{C1'-C2'}$	$\sigma^*_{C3'-O3'}$	5.03						
		Σ	**127.35**		**Σ**	**125.00**		**Σ**	**105.13**		**Σ**	**124.70**		**Σ**	**65.72**		**Σ**	**66.57**

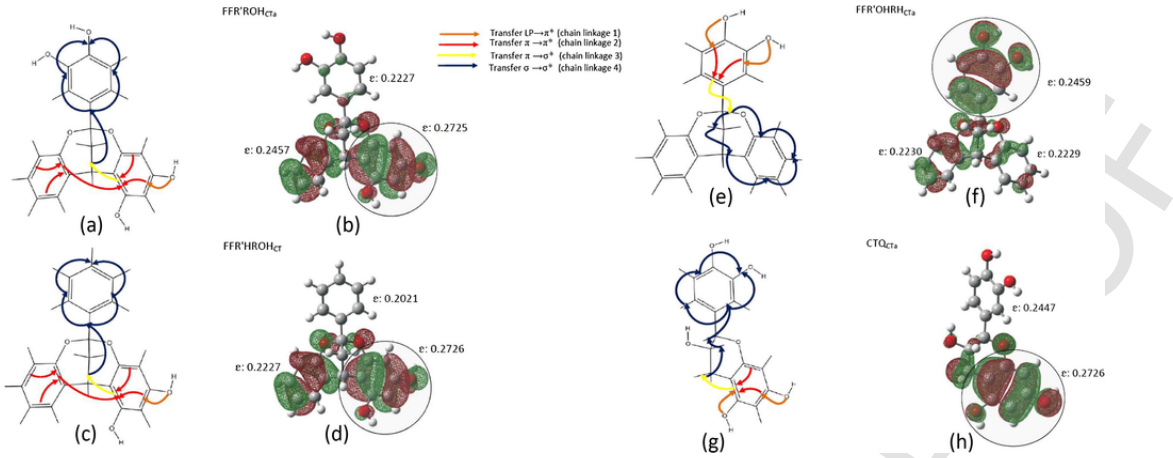

Fig. 4. Charge delocalization routes modeling the π-electron system interaction of resorcinol/catechol ring with the rest of the structure in gas phase, and related to IP value. (a), (c), (e) and (g): Graphical representation of the "$\pi \rightarrow \sigma$ *delocalization route*" descriptor. $LP \rightarrow \pi^*$ delocalization is indicated in orange; $\pi \rightarrow \pi^*$ in red; $\pi \rightarrow \sigma^*$ in yellow, and $\sigma \rightarrow \sigma^*$ in blue. (b), (d), (f) and (h): HOMO distribution in gas phase obtained by TZ calculation scheme. Ellipticity (ε) values for each calculated ring at the same level of theory are indicated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

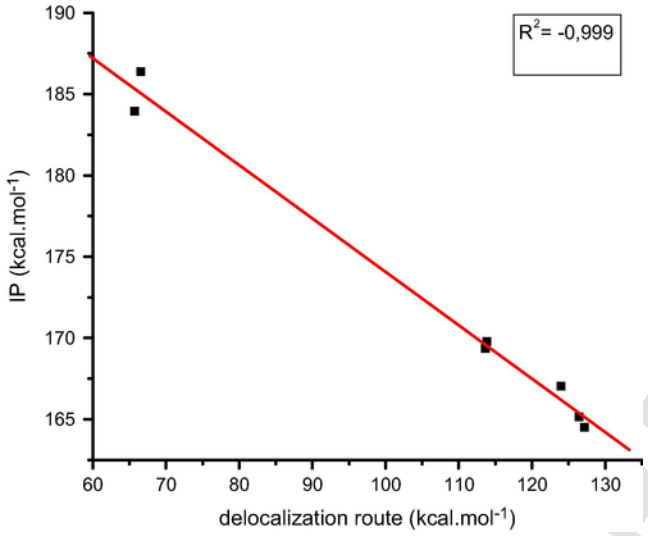

Fig. 5. Relationship between IP values, and charge transfers associated with the "$\pi \rightarrow \sigma$ *delocalization route*" descriptor discussed in the text. Correlation coefficient R^2 for linear fit 0.999.

necessary considering delocalizations in the rest of the electronic distribution. If this mechanism is also considered as rationalized in two stages, our results indicate that the O—H homolytic cleavage is strongly dependent only on the First Stage, e.g., hydrogen atom donation to FR; the second stage (antioxidant structure stabilization after H lost) being similar in all cases and/or not required for BDE description, at least in the studied set where structural similarity is high. This is no longer true when analyzing IP trends, which could be anticipated by the IP variations of the various structures that are higher than BDE variations. Therefore, structural variations, although small, are important when studying SET reaction.

4. Conclusions

In this paper 30 structures were especially selected due to structural variations with each other, and further analyzed. These structures account for minimum energy configurations of conformational spaces previously studied in our laboratories. In the present paper the ability of the structures to scavenge free radicals is modeled, considering HAT and SET mechanisms by calculating BDE and adiabatic IP. Two new indicators arising from electronic delocalizations in the structures are proposed: These indicators may predict which compounds offer the best antioxidant ability by analyzing only the parent molecule.It is concluded that:

- The "*O—H bond donor role*" descriptor ($\sigma_{O—H} \rightarrow \sigma^*_{C—C}$ delocalization) is useful to analyze BDE trends of the corresponding O—H bond.
- The electron charge delocalization ($\sigma_{O—H} \rightarrow \sigma^*_{C—C}$) associated with such descriptor decreases when BDE value improves (also decreases), i.e., when the ease of the antioxidant to donate a hydrogen atom to a FR increases.
- The second-order energy associated with $\sigma_{O—H} \rightarrow \sigma^*_{C—C}$ donor-acceptor interaction decreases due to the overlap decrease of these natural orbitals.
- The associated donor-acceptor interaction decreases mainly due to changes in the acceptor natural orbital ($\sigma^*_{C—C}$).
- The BDE is smaller, the lower the "*s*"-type contribution of the substituted carbon atom is in the hybridization of the C—C acceptor natural orbital.
- The C-O bond length associated with the O-H bond that will undergo homolytic cleavage also correlates with BDE values in agreement with results of other compounds reported by other authors.
- The C—O bond length associated with the O—H bond that will undergo homolytic cleavage also correlates with BDE values in agreement with results of other compounds reported by other authors.
- The "*O—H bond donor role*" descriptor turns out to be of higher quality (better correlation coefficient) than C—O bond length, in describing FR scavenging by HAT modeled by BDE calculations.
- The "*O—H bond donor role*" descriptor is presented as a "local" indicator on the set of studied structures.
- The "$\pi \rightarrow \sigma$ *delocalization routes*" descriptor is useful to analyze IP trends.
- The electron charge transfer associated with delocalization routes defined in the above descriptor increases when IP value enhances, e.g., when the ease of antioxidant electron donation to FR by SET mechanism increases.

– The π-electron system charge transfers in one of the rings are relevant for the "$\pi \rightarrow \sigma$ *delocalization routes*" descriptor, which is considered the reactive ring for SET reaction.
– The reactive ring is also that in which the highest HOMO distribution and average ellipticity are found.
– The reactive ring is a substituted one, and the descriptor also shows the importance of substituents contribution to π-electron system population of such ring.
– The increased π-electron system charge delocalization of the reactive ring is correlated with IP decrease, i.e., with increased system reactivity against SET reaction.
– The "$\pi \rightarrow \sigma$ *delocalization route*" descriptor for IPs is presented as a "non-local" indicator on the set of studied structures, even if structural similarity is high.
– The "$\pi \rightarrow \sigma$ *delocalization route*" descriptor for IPs leads to the analysis of SET reaction in two stages:

First stage, "to donate the electron to FR": it is concluded that it is important to have a π-enriched ring, from which FR will take the electron; in this step is significant the presence of substituents increasing electron availability in the π-system of the ring.

Second stage, "to stabilize the structure after the electron loss": we conclude that it is important to have a good possibility of electron charge delocalization of the own π-electron distribution. This stage is defined by the effectiveness of the antioxidant structure for charge transfer, available for electronic distribution stabilization after the disturbance suffered by FR interacting.

– The σ-electron system delocalization routes modeling ring interactions are more effective in flavans that in CTQ.

Finally, our results validate the use of the so-called MIX calculation (optimized geometries, ZPE and CTE corrections obtained with 6-31G(d,p) basis set, and subsequent AIM/NBO analysis with 6-311++G(d,p) basis set by single-point calculations) to obtain reliable results for BDE thermodynamic parameter; minimizing computational costs if necessary. This is important given our interest in larger antioxidants (other naturally-occurring flavonoids) or by the calculation complexity, i.e., to study the kinetics and modeling in solution of the proposed reactions, which is the subject of current development in our laboratories.

The study of solvent effects on the new indicators arising from electron delocalizations is of great interest, and requires a deeper analysis since both polar and non-polar solvents must be taken into account. This study is in progress, and will be reported in the near future.

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Appendix A. Supplementary material

See supplementary material for the "$\pi \rightarrow \sigma$ *delocalization route*" descriptor for b-type structures and the corresponding donor-acceptor interactions and second order stabilization energies $E^{(2)}$ from NBO study calculated at B3YP/6-311++G(d,p) level of theory. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.comptc.2017.03.028.

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