What is Important to Prevent Oxidative Stress? A Theoretical Study on Electron-Transfer Reactions between Carotenoids and Free Radicals

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Oxidative stress is related to the development of a large number of health disorders. Therefore, the study of molecular systems capable of preventing its onset by fighting free radicals is a crucial area of research. Carotenoids are one of the most efficient families of compounds fulfilling this purpose. In the present work, the free-radical-scavenger efficiency, expressed as the one-electron-donating capability, of different carotenoids has been studied using density functional theory. A large number of free radicals were considered, as well as environments of different polarity. A new donor–acceptor map is proposed that allows a rapid evaluation of full electron-transfer processes. Its efficiency for predicting the feasibility of electron transfer (ET) between carotenoids and free radicals was tested and validated through comparison with the corresponding Gibbs free energies of reaction. Our results demonstrate that ET reactions between carotenoids and free radicals are strongly influenced by the nature of the latter. Moreover, it is proposed that the electron affinity (EA) of the reacting free radical has an important effect on the viability of these reactions. The reactions were found to become exergonic when the EA of the free radical involved reaches a value of ~5 eV.

Introduction

Oxidative stress can be defined as the imbalance between biochemical processes, leading to the production of reactive oxygen species (ROS) and species responsible for their removal.[1] In the past few decades, oxidative stress has attracted a great deal of attention because of the increasing evidence supporting its role in the development of a large number of health disorders.[2] Because oxidative stress involves reactions between biological molecules and free radicals, the study of compounds with free-radical-scavenging activity becomes an important area of research aiming to prevent oxidative stress and the consequent molecular damage.

One family of compounds that stands out for their free-radical-scavenging ability are carotenoids (CARs).[3,4] They are naturally occurring pigments frequently present in the human diet and in many living organisms.[5] There are three viable mechanisms generally accepted for their reactions with free radicals:[6] electron transfer (ET), radical adduct formation, and hydrogen-atom transfer. The relative importance of the different reaction channels depends on diverse factors including the nature of the reacting free radical; the structural features of the CAR;[7,8] and in biological systems, the location and orientation of the CAR within the membrane.[8] In the present work, we focus only on the ET mechanism. Therefore, the study of the electron-donating and electron-accepting capabilities of the involved species acquires particular relevance.

A straightforward way of analyzing the relative feasibility to donate, or accept, charge among a set of chemical compounds

has recently been presented[9] and successfully used.[10,11] It is known as the donor–acceptor map (DAM), and it is constructed from electron acceptance and electron donation indexes.[9] These indexes are based on electron-accepting and electron-donating powers[12] and are defined relative to fluorine and sodium, respectively. So far, this mapping process has been used to analyze the intrinsic radical-scavenging capabilities of a variety of compounds. However, free radicals have not been included in the analyses. Because the nature of the reacting free radical is so crucial that it can even invert the relative importance of the free-radical-scavenging mechanisms,[13] it seems imperative to include free radicals within the DAM. It is important to remember that, to scavenge free radicals, the electron-transfer process of radical scavengers involves a single electron transfer. The electron-donating and electron-accepting power indexes described previously by Gazquez et al.[12] are useful for describing the propensity of a given chemical species to donate or accept fractional amounts of charge. To consider full electron-transfer processes and to characterize the capacity to donate or accept electrons, vertical ionization energies (IEs) and electron affinities (EAs) would be better indexes. For this reason, as well as for the purpose of analyzing the electron-transfer process of radical scavengers and free radicals, we define a new DAM considering IEs and EAs called the full-electron donor–acceptor map (FEDAM).

It is the main aim of the present work to validate the predictions of the FEDAM when the free radicals are explicitly included in the comparison. For that purpose, the reactions of several carotenoids with a large set of free radicals have been computed. The validity of the predictions from the FEDAM analysis is tested by comparison with the corresponding adiabatic Gibbs free energies of reaction. The influence of the polarity of the environment on the viability of ET has also been taken into account. General conclusions based on the nature of

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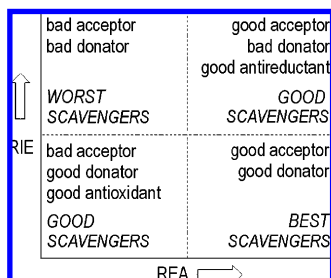
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Figure 1. Full-electron donor−acceptor map (FEDAM). For the definitions of RIE and REA, see eqs 1 and 2.

the free radicals are drawn. The applicability of the new mapping scheme is analyzed based on the nature of the ET reaction.

Definition of the Full-Electron Donor−Acceptor Map (FEDAM) and Computational Details

To understand the radical-scavenging capacity of different molecules, it is important to study the one-electron-transfer process considering also their capacity to accept electrons. For this purpose, IEs and EAs are the most evident properties to consider. It is also important to make comparisons with other well-known antioxidant and antireductant substances. For this reason, values of IE and EA for F and Na atoms (obtained at the same level of theory) were used to obtain the corresponding relative values of electron acceptance (REA) and electron donation (RIE) indexes. These quantities were defined according to the equations

$$RIE = \frac{IE_L}{IE_{Na}} \quad (1)$$

$$REA = \frac{EA_L}{EA_F} \quad (2)$$

where L represents the considered molecule.

From these values, it is possible to construct a new DAM, called the FEDAM (Figure 1). It is built up as a plot of RIE vs REA and provides useful information to classify any substance L regarding its electron-donating/-accepting capabilities, when the electron-transfer process involves full electron movement from one molecule to another. In the present work, we use the new FEDAM to analyze the one-electron-transfer mechanism between CARs and free radicals.

Full optimizations without symmetry constraints were carried out using the hybrid three-parameter B3LYP functional[14] within the density functional theory (DFT) framework and the 6-311G(d) basis set.[15] Harmonic frequency analyses were used to verify the optimized minima. Single-point energy calculations at these optimized geometries were performed with the same functional and the 6-311+G(d)[15] basis set to obtain vertical IEs and EA. Adiabatic IEs and EAs were also computed at the B3LYP/6-311+G(d)//6-311G(d) level of theory.

Thermal corrections to the Gibbs free energies of the B3LYP/6-311G(d) fully optimized stationary points plus the corresponding B3LYP/6-311+G(d) single-point electronic energies were used to obtain the adiabatic Gibbs free energy of each species involved in the charge-transfer reaction. The stationary points were first modeled in the gas phase (vacuum), and solvent effects were included a posteriori by single-point calculations using the polarizable continuum model (PCM), specifically the
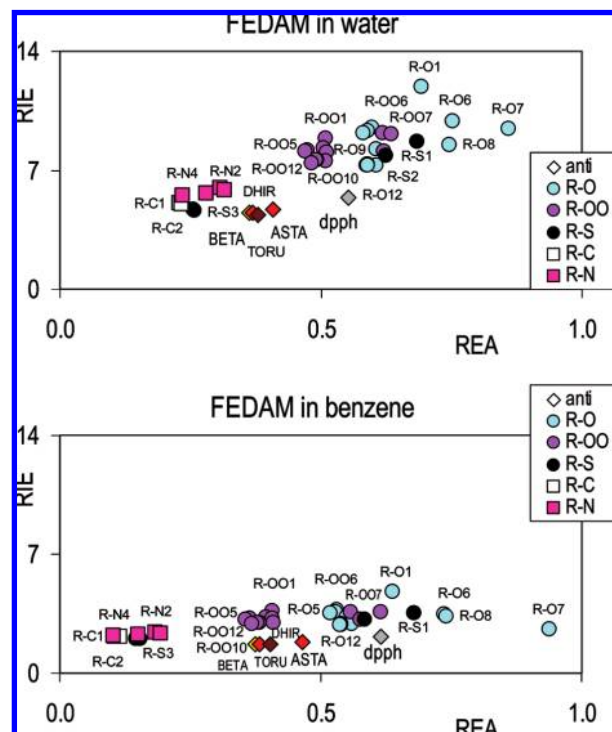

Figure 2. FEDAM of radicals and radical scavengers studied in this work in water and benzene as solvents.

integral equation formalism (IEF-PCM)[16] at the B3LYP/6-311+G(d) level of theory, with water and benzene as the solvents for polar and nonpolar environments, respectively. All calculations were done with Gaussian 03 software.[17] The Gibbs free energies in solution were, in turn, computed as the PCM B3LYP/6-311+G(d) single-point electronic energies plus the thermal corrections to the Gibbs free energies from the gas-phase B3LYP/6-311G(d) calculations.

Results and Discussion

FEDAM. It was proposed in a previous work[9] that CARs might scavenge free radicals by either donating or accepting electrons. It was also established that, to analyze the radical-scavenging capacity of these molecules, it is necessary to consider the electron donor−acceptor capacities of the free radicals. To this end, in Figure 2, we report the FEDAM in water and benzene for four radical scavengers and more than 30 free radicals, including several of the most important for biological systems, namely, peroxyl (R−OO) and alkoxyl (R−O) radicals. The FEDAM for the gas phase is provided as Supporting Information for comparison purposes only, as the studied carotenoids are not expected to occur in the gas phase. In addition to R−OO and R−O, free radicals with nitrogen, carbon, and sulfur in their structures were also considered. 2,2-Diphenyl-1-picrylhydrazyl (DPPH) was included in this study because it is frequently used in experiments designed to investigate radical−molecule reactions. The studied carotenoids were β-carotene (BETA), astaxanthin (ASTA), torulene (TORU), and 3,3′-dihydroxyisorenieratene (DHIR). Results for BETA and ASTA were partially reported before (see ref 9). TORU has recently been proposed as the most easily oxidized CAR in polar and nonpolar solvents,[18] and DHIR is a CAR with an unusual structure that was reported to have superior antioxidant and photoprotective properties.[19] The radical scavengers and free radicals considered in this study are shown in Figure 3.

As shown in Figure 2, all of the studied species are much better electron acceptors (have higher REAs) in water than in
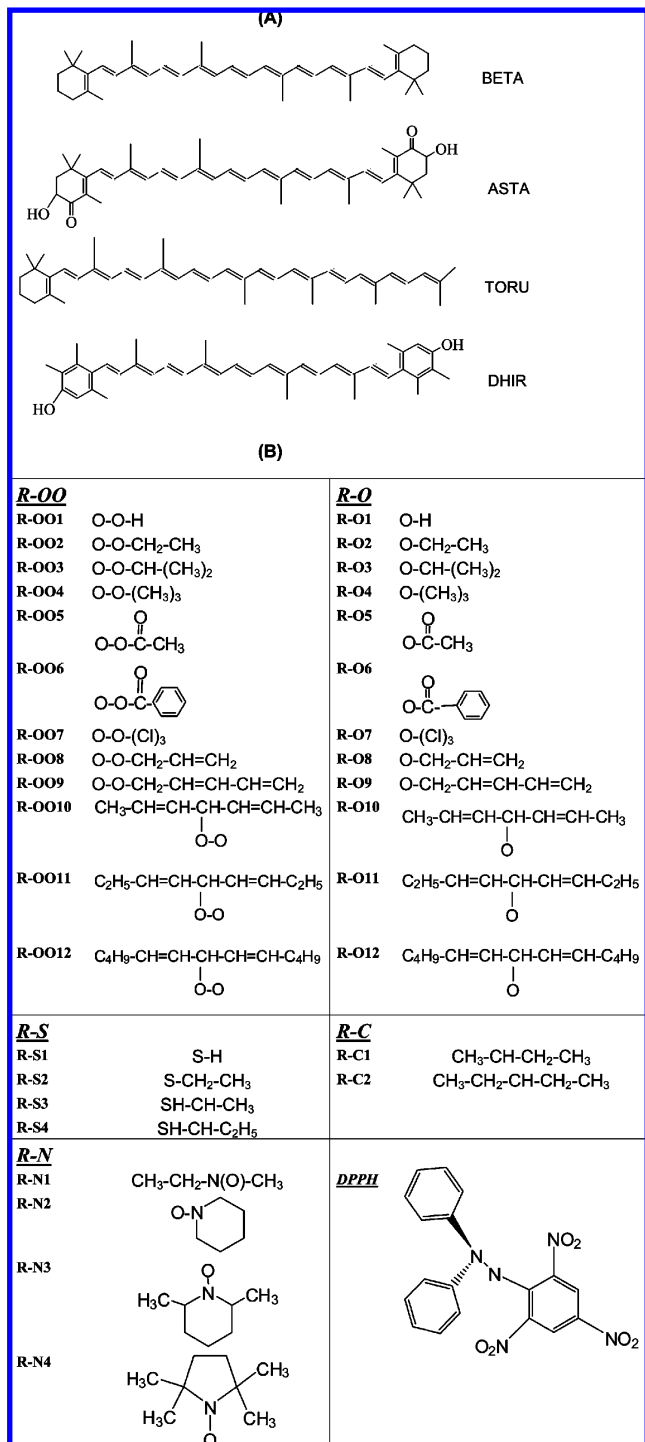
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**Figure 3.** Sets of (A) radical scavengers and (B) free radicals studied in this work.

benzene. The electron donor−acceptor properties of free radicals are closer to those of the radical scavengers in benzene than they are in water. As was previously reported for the DAM,[9] the FEDAM is a powerful tool that allows for the classification of any substance according to its electron donor−acceptor capacity. Both the DAM and FEDAM are simply maps that allow for the analysis of the relative acceptor and donor abilities of each pair of reacting species, that is, each radical−CAR pair in the present study. It seems worth emphasizing that these maps are not correlations and that there is no reason to expect the data to follow a linear tendency. These maps should be read

pair to pair, and attention must be paid to the relative positions of the two reactants in the map.

As the FEDAM shows (Figures 1 and 2), carotenoids are located in the good-electron-donors section of the map because most of the free radicals that are reported in this work are better electron acceptors and worse electron donors than CARs (REAs and RIEs are larger for free radicals than for CARs). Accordingly, the electron-transfer mechanism that is expected to prevail for radical scavengers (anti) scavenging free radicals (R) corresponds to

$$\text{anti} + R^\bullet \rightarrow \text{anti}^{\bullet+} + R \tag{I}$$
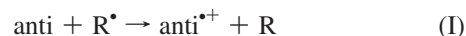
However, there are some free radicals (R−C and R−N) that are worse electron acceptors than CARs. In this case, the radical scavengers might accept electrons according to the reaction

$$\text{anti} + R^\bullet \rightarrow \text{anti}^{\bullet-} + R^+ \tag{II}$$
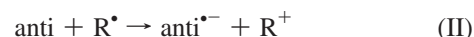
Analysis of the FEDAM indicates that both mechanisms are feasible for scavenging free radicals: the radical scavengers can lose or donate an electron to deactivate the free radical, and apparently, the reaction depends on the characteristics of the free radical rather than on the nature of the CAR.

To determine whether the predictions of the electron-transfer reactions from the FEDAM are correct, it is necessary to perform a more detailed study. To this end, the energy evolution associated with the electron-transfer process between each pair of studied CARs and free radicals was computed as the corresponding adiabatic Gibbs free energy at 298 K.

Adiabatic Gibbs Free Energies. For reaction I, the adiabatic Gibbs free energy was calculated according to

$$\Delta G^0_{\text{ET}} = [G(\text{anti}^{\bullet+}) + G(R^-)] - [G(\text{anti}) + G(R^\bullet)] \tag{3}$$

whereas for reaction II, this calculation corresponds to

$$\Delta G^0_{\text{ET}} = [G(\text{anti}^{\bullet-}) + G(R^+)] - [G(\text{anti}) + G(R^\bullet)] \tag{4}$$

The results of the adiabatic Gibbs free energies for both reaction schemes are reported in Table 1 for water and benzene solutions. Vertical and adiabatic IEs and EAs are provided as Supporting Information. As the values in Table 1 show, both reactions I and II of CARs with free radicals are endergonic in benzene with only one exception (R−O7). Accordingly, it seems that the ET mechanism is unlikely to occur in nonpolar environments. This is a logical finding given that ET mechanisms lead to the formation of ions, which are expected to be stabilized though electrostatic interactions with the surrounding molecules of solvent. Therefore, a nonpolar solvent is not the proper environment to stabilize the charged species that are formed. A comparison between the Gibbs free energies of reaction in solution and in the gas phase (reported in Supporting Information) shows that the presence of the solvents increases the viability of the electron-transfer processes. This effect is larger for water than it is for benzene, which is a logical finding because the reaction products are charged species. Even though the magnitude of the solvent effects depends on the nature of the reacting system (carotenoid and radical), the average

TABLE 1: Adiabatic Gibbs Free Energy (ΔG, kJ/mol) at 298.15 K for Reactions *I* and *II* between Radicals and Radical Scavengers from Figure 3 in Water and Benzene Solutions[a]

	reaction I anti + R• → anti•+ + R−				reaction II anti + R• → anti•− + R+			
	BETA	ASTA	TORU	DHIR	BETA	ASTA	TORU	DHIR
				water				
DPPH	−29.3	−12.6	−35.6	−13.0	252.7	215.5	239.3	250.2
R−OO1	19.7	36.8	13.8	36.4	530.1	492.9	516.7	527.6
R−OO2	22.6	39.7	16.7	39.3	483.3	446.0	469.9	481.2
R−OO3	50.6	67.8	44.8	67.4	456.5	419.2	443.1	454.0
R−OO4	53.1	69.9	46.9	69.5	434.3	396.6	420.5	431.8
R−OO5	−58.2	−41.4	−64.4	−41.8	436.0	398.7	422.6	433.9
R−OO6	−59.8	−43.1	−66.1	−43.1	411.7	374.5	398.3	409.2
R−OO7	−83.3	−66.5	−89.5	−66.9	473.2	435.6	459.8	470.7
R−OO8	28.9	45.6	22.6	45.6	457.3	420.1	443.9	454.8
R−OO9	31.4	48.1	25.1	48.1	405.0	367.8	391.6	402.9
R−OO10	47.7	64.4	41.4	64.0	334.7	297.5	321.3	332.2
R−OO11	56.1	72.8	49.8	72.4	330.5	293.3	317.1	328.0
R−OO12	64.9	81.6	58.6	81.2	327.2	290.0	313.8	325.1
R−O1	−69.0	−51.9	−74.9	−52.3	877.0	839.7	863.6	874.5
R−O2	3.3	20.5	−2.1	20.1	153.6	116.3	140.2	151.0
R−O3	−2.1	14.6	−7.9	14.2	43.9	6.7	30.5	41.8
R−O4	−0.4	16.3	−6.7	15.9	91.6	54.8	78.7	89.5
R−O5	−142.7	−125.9	−149.0	−126.4	581.6	544.8	568.2	579.1
R−O6	−144.8	−127.6	−151.0	−128.0	531.8	494.1	518.4	529.3
R−O7	−264.4	−247.3	−270.3	−247.7	414.6	378.2	401.2	412.1
R−O8	−13.4	2.9	−19.7	2.9	40.6	3.3	27.2	38.5
R−O9	−10.5	5.9	−16.7	5.9	112.5	75.3	99.2	110.0
R−O10	−13.4	2.9	−19.7	2.9	76.6	38.9	63.2	74.1
R−O11	−13.4	2.9	−19.7	2.5	73.6	36.4	60.2	71.1
R−O12	−10.5	6.3	−16.7	5.9	66.5	29.3	53.1	64.4
R−S1	−62.3	−45.6	−68.6	−45.6	570.7	533.5	557.3	568.2
R−S2	−21.8	−4.6	−27.6	−5.0	175.3	137.7	161.5	172.8
R−S3	170.7	187.4	164.0	187.0	143.9	106.7	130.5	141.4
R−S4	171.5	188.3	165.3	187.9	140.2	102.9	126.8	137.7
R−C1	217.1	234.3	210.9	233.9	183.7	146.0	170.3	181.2
R−C2	217.6	234.7	211.3	234.3	184.5	147.3	171.1	182.0
R−N1	132.6	149.4	125.9	149.0	241.8	204.2	228.0	239.3
R−N2	123.8	140.2	117.2	140.2	231.8	194.6	218.4	229.3
R−N3	163.6	180.3	157.3	179.9	229.3	192.0	215.9	226.8
R−N4	194.6	211.3	188.3	210.9	231.0	193.7	217.6	228.4
				benzene				
DPPH	70.3	101.3	45.6	81.6	382.8	328.0	379.9	393.3
R−OO1	200.4	231.4	175.3	211.7	740.1	685.8	737.6	751.0
R−OO2	207.5	238.5	182.8	219.2	640.2	585.8	637.6	651.0
R−OO3	226.8	257.7	202.1	238.5	608.8	554.4	606.3	619.7
R−OO4	229.3	260.2	204.2	240.6	574.0	519.7	571.5	584.9
R−OO5	115.9	146.9	91.2	127.2	592.5	537.6	589.9	603.3
R−OO6	107.5	138.5	82.8	119.2	551.0	496.6	548.5	561.9
R−OO7	65.3	96.2	40.6	77.0	630.1	575.7	627.6	641.4
R−OO8	207.9	238.9	182.8	219.2	607.5	553.1	605.0	618.4
R−OO9	200.4	231.4	175.3	211.7	546.8	492.5	544.3	557.7
R−OO10	222.2	253.1	197.1	233.5	464.4	410.0	461.9	475.3
R−OO11	227.6	258.6	202.5	238.9	459.0	404.6	456.5	469.9
R−OO12	235.1	266.1	210.5	246.9	449.4	395.0	446.9	460.2
R−O1	119.7	150.6	95.0	131.0	1108.8	1054.8	1106.7	1120.1
R−O2	173.6	204.6	149.0	185.4	315.5	261.1	313.0	326.4
R−O3	164.4	195.4	139.7	175.7	208.8	154.0	205.9	219.2
R−O4	164.8	195.8	139.7	176.1	230.5	175.7	227.6	241.0
R−O5	22.2	53.1	−2.5	33.9	741.0	686.6	738.5	751.9
R−O6	10.5	41.4	−14.2	22.2	673.6	619.2	671.1	684.5
R−O7	−133.1	−102.1	−157.7	−121.3	577.4	523.0	574.9	588.3
R−O8	153.1	184.1	128.4	164.8	215.9	161.1	213.0	226.8
R−O9	149.8	181.2	125.1	161.5	262.8	208.4	260.2	273.6
R−O10	148.5	179.5	123.8	160.2	205.4	150.6	202.9	216.3
R−O11	154.8	185.8	129.7	166.1	197.9	143.1	195.0	208.4
R−O12	152.7	183.7	128.0	164.4	198.7	143.9	195.8	209.2
R−S1	97.9	128.9	73.2	109.6	769.0	714.6	766.5	779.9
R−S2	147.3	178.2	122.6	159.0	342.7	288.3	340.2	353.5
R−S3	317.1	348.1	292.5	328.9	306.3	251.9	303.8	317.1
R−S4	315.5	346.4	290.4	326.8	300.8	246.0	298.3	311.7
R−C1	371.5	402.5	346.9	383.3	341.8	287.0	338.9	352.3
R−C2	368.2	399.2	343.5	379.9	338.1	283.7	335.6	348.9
R−N1	301.2	332.2	276.6	312.5	384.5	329.7	381.6	395.4
R−N2	297.1	328.0	272.4	308.8	370.3	315.5	367.8	381.2
R−N3	327.2	358.2	302.5	338.9	360.7	306.3	358.2	371.5
R−N4	347.7	378.7	323.0	359.0	353.5	298.7	350.6	364.0

[a] Geometry optimizations performed at the B3LYP/6-311G(d) level. Final energy evaluation obtained from a single point for neutral, anion, and cation at the B3LYP/6-311+G(d) level.

lowering in ΔG for aqueous solutions, with respect to the gas phase, is twice that for benzene solutions.

On the other hand, the Gibbs free energies of one-electron transfer from CARs to free radicals in water solutions were found to be exergonic for several free radicals when the reaction takes place through path **I**. Therefore, these free radicals are expected to react by the ET reaction, with the charge transfer occurring from the CAR toward the radical. The results for the Gibbs free energy corresponding to ET in the opposite direction, that is, from the free radical to the CAR (reaction II), were found to be endergonic for all of the studied reactions, indicating that path II is not viable in water.

As can be seen in Figure 2 (for water and benzene), the RIE values indicate that radical scavengers are better electron donors (smaller RIEs) than R−O, R−OO, and some R−S groups, but they have electron donor capabilities similar to those of R−C and R−N. Concerning the electron acceptor capabilities, the REA values indicate that R−C and R−N have values similar to those of radical scavengers in water. In benzene, R−C, R−N, R−OO, and radical scavengers have comparable REA values. According with the FEDAM shown in Figure 2, reaction II is unlikely because most of the studied free radicals are worse electron donors than any of the modeled radical scavengers. Thus, free radicals will not donate one electron to the scavengers. To analyze reaction I, one must consider the electron-acceptor capacity of the free radicals. As shown in Figure 2, most of the studied free radicals are better electron acceptors (have larger REAs) than the radical scavengers. The exceptions are R−C and R−N. The adiabatic Gibbs free energies reported in Table 1 (for water) indicate that reaction I for the free radicals with larger REAs are exergonic, which reasonably agrees with the predictions from the FEDAM. In water, R−C and R−N have electron-acceptor properties similar to those of the radical scavengers but they are worse electron donors, and for this reason, the adiabatic Gibbs free energies indicate that both reactions are endergonic for these free radicals. In benzene, this is also the case for most of the free radicals modeled in this study. Apparently, the only free radical that has enough electron-acceptance capability to react in benzene with the radical scavengers shown in Figure 3 is R−O7.

One of the mechanisms discussed in the literature for radical scavenging is the one-electron-transfer reaction. The FEDAM is a better representation than the previously reported DAM for studying the radical-scavenging capacity of any substance in terms of ET, because this process involves full, not partial, electron transfer. IE and EA are just the properties of a system that measure its propensity to donate or accept one electron. Predictions from the newly proposed FEDAM are supported by the good agreement with the adiabatic Gibbs free energy values.

Comparison between Radical Scavengers. The adiabatic Gibbs free energy values corresponding to the ET reactions involving all of the radical scavengers and free radicals considered in this study are reported in Table 1. As these values show, the reactivity order (starting from the most negative adiabatic ΔG value) for reaction I is

$$TORU > BETA > ASTA \approx DHIR$$

that is, TORU is the best radical scavenger, whereas ASTA and DHIR are the worst. Moreover, BETA is a better radical scavenger than ASTA, and DHIR, the new CAR recently reported as the best one, apparently is not as good at donating electrons as TORU and BETA.
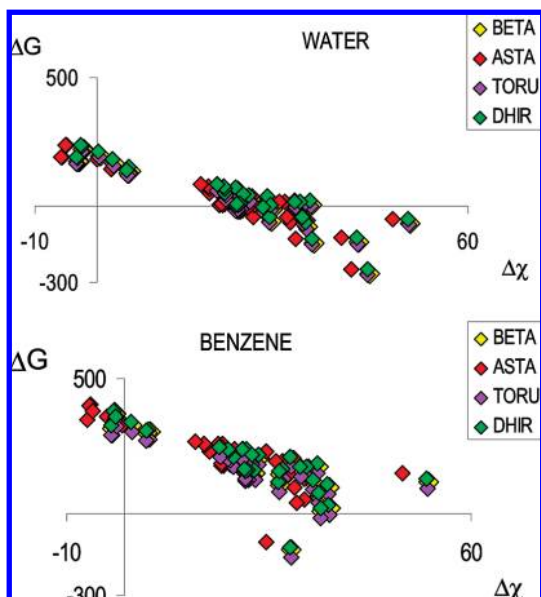
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Figure 4. ΔG at 298.15 K for reaction I in water and benzene, as a function of the eletronegativity difference ($\Delta\chi$) between the free radical and the radical scavenger. ΔG values are in kJ/mol, and $\Delta\chi$ values are in eV multiplied by 10 for a better scale.

It can be thought that the reactivity order for reaction I should correlate with the IEs of the radical scavengers. Generally, low values of IE indicate that the molecule is a better radical scavenger because the energy that is necessary to remove one electron is small, so that it can scavenge free radicals by electron donation. However, in this case, the order in IEs (ASTA > BETA ≈ DHIR > TORU; Supporting Information) does not correspond with the reactivity order, because when this analysis is performed alone, the role of the free radical is ignored.

Even though there is not a direct correlation between ΔG and IE, it is possible to state that the lowest IE corresponds to the most negative value of ΔG. It is important to remember that BETA is considered a yellow pigment, whereas ASTA is a red one.[5] There is the idea that red CARs are better antioxidants than yellow ones. However, from the results of this work, it seems that yellow CARs act as better antioxidants molecules than red ones. Notwithstanding the existence of a correlation between IE and ΔG, it is clear from the results in Table 1 that knowledge of the radical scavengers' properties alone it is not enough to predict the reactivity order for the charge-transfer process.

Electronegativity and Hardness. In this section, we consider only reaction I, as reaction II was previously ruled out for most of the studied radicals. Apparently, to scavenge free radicals through the ET mechanism there must be a balance between the electron-donor and electron-acceptor capacities of the reactants. One reactivity index that is able to measure this balance is the electronegativity (χ). In this sense, electronegativity indicates the tendency of a system to gain or lose electrons. It is well-known that electron-transfer reactions are favored when the difference between the reactants' electronegativities ($\Delta\chi$) is large. Therefore, it seems logical to assume that there must be some relationship between $\Delta\chi$ and ΔG of ET processes. A plot of ΔG versus $\Delta\chi$ is shown in Figure 4. The electronegativity of each species was calculated as

$$\chi = \frac{IE + EA}{2} \qquad (5)$$

from the corresponding vertical ionization energy (IE) and vertical electron affinity (EA) of each species. $\Delta\chi$ is the χ value of the free radical (rad) minus the χ value of the radical scavenger (anti). As can be seen in the figure, there is no direct correlation between these two variables. There are some systems that have large values of $\Delta\chi$ but, nevertheless, have adiabatic Gibbs free energy values that indicate that the reaction is endergonic. This is more evident in benzene than in water, but in both cases, it is not possible to say that $\Delta\chi$ is an index that can be used to predict the adiabatic Gibbs free energy tendency.

Another chemical index that can be useful in the analysis of charge-transfer reactions is the hardness (η). This parameter measures the resistance to the flow of electrons and is well-defined in the density functional theory framework as

$$\eta = IE - EA \qquad (6)$$

$\Delta\eta$ is then defined similarly to $\Delta\chi$, that is, as the η value of the free radical (rad) minus the η value of the radical scavenger (anti). Once again in this case, no direct correlation with ΔG was found (not shown).

$\Delta\chi$ and $\Delta\eta$ by themselves do not follow the same reactivity trend as ΔG for ET reactions. To obtain an index than can be correlated with ΔG, it is possible to use the difference between the reactants' electronegativity (χ, a measure of the ability to accept electrons) together with the difference in hardness (η, a measure of the resistance to donate electrons). With these two quantities, a new descriptor (called the full-electron transferability index, $\Delta\Theta$) can be empirically defined as

$$\Delta\Theta = \Delta\chi - \Delta\eta = \frac{1}{2}(IE_{anti} - IE_{rad}) + \frac{3}{2}(EA_{rad} - EA_{anti}) \qquad (7)$$

This descriptor provides a measure of the feasibility of the charge-transfer mechanism, simultaneously considering both the electron-donor capacity of the radical scavenger (relative to the radical) and the electron-acceptor capability of the free radical (relative to the radical scavenger). A plot of ΔG versus $\Delta\Theta$ (Figure 5) shows that there is a nice correlation between these two quantities in water and benzene solutions. The largest discrepancies from linearity were found for plotted values that are close to zero, which is expected because of the known uncertainty of the calculations. It seems that $\Delta\Theta$ is a quantity that retains the correct relative order of reactivity and that it can be reliably used to predict the viability of ET reactions. It is important to note that this quantity is calculated at a significant lower computational cost than ΔG. However, when ΔG is small, it is not possible to use $\Delta\Theta$ because of the uncertainty of the calculations.

What is Important to Prevent Oxidative Stress? The key condition for biological radical-scavenging systems is that they should lessen, rather than exacerbate, the effects of oxidative stress, and they should not generate toxic byproducts as a result of their function. One of the mechanisms for reducing oxidative stress is the electron-transfer process, which is very useful for scavenging free radicals. To determine whether there is a key parameter that controls the radical-scavenging system through this mechanism, we can analyze the characteristics of the reacting free radicals. From those values, it is possible to establish that ET reactions are controlled not only by the nature of the radical scavenger, but also, and to a larger extent, by the nature of the radical. The reaction actually becomes endergonic
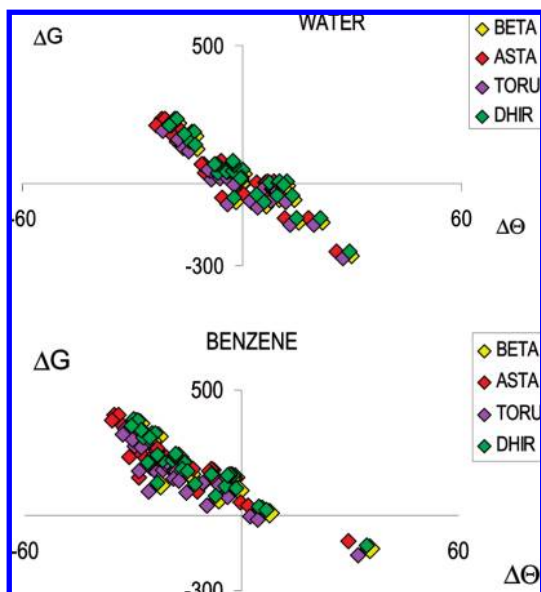
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Figure 5. ΔG at 298.15 K for reaction I in water and benzene, as a function of $\Delta\Theta$, defined in eq 7. ΔG values are in kJ/mol, and $\Delta\Theta$ values are in eV multiplied by 10 for a better scale.
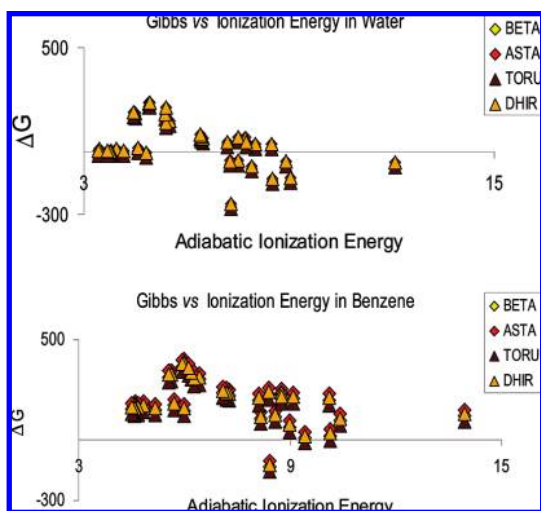

Figure 6. ΔG for reaction I at 298.15 K in water and benzene versus the adiabatic ionization energy of the reacting free radical. ΔG values are in kJ/mol, and IEs are in eV.

or exergonic depending on the free radical with which the carotenoids are reacting. To explore this hypothesis, the adiabatic Gibbs free energies versus the IEs and EAs of the free radicals are plotted in Figures 6 and 7. As these figures show, there is no correlation between ΔG and IE, but EA correlates well with ΔG. This means that the reaction is strongly influenced by the capacity of the free radical to accept an electron and that the capacity of the radical scavenger to donate electrons is less important, provided that the radical scavenger belongs to the subset of chemical compounds that are good electron donors. This becomes evident from eq 7, where the weight of EA is 3 times that of IE.

Accordingly, it seems reasonable to state that all CARs (yellow, red, or the best carotenoid reported before) have more or less the same capability to scavenge free radicals. Apparently, the condition to have an exergonic reaction between a CAR and a free radical is that the EA of the free radical should be equal to or larger than 5 eV. It should be noted that this condition is valid for the studied radical scavengers, because all of them
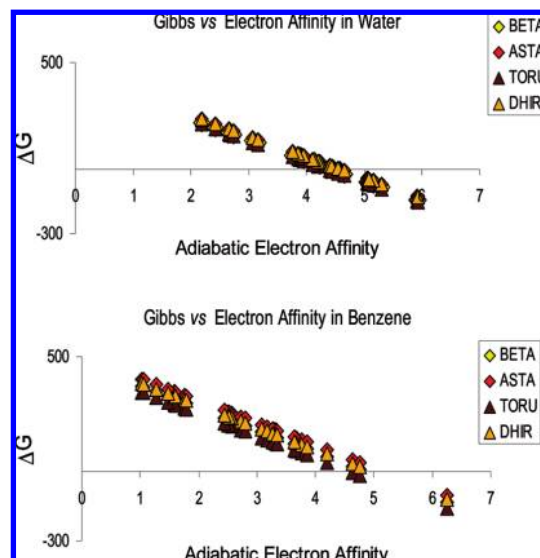

Figure 7. ΔG at 298.15 K for reaction I in water and benzene, as a function of the adiabatic electron affinity. ΔG values are in kJ/mol, and EAs are in eV.

are good electron donors. To determine whether this condition is general for any radical-scavenging substance, more theoretical studies considering other radical-scavenging substances are necessary.

In a previous work,[9] we proposed that CARs could play their radical-scavenging role by accepting electrons from free radicals, that is, oxidizing free radicals. However, the comparison between the electron donor−acceptor capabilities of CARs and those of free radicals indicates that this mechanism is unlikely. From the results of the present work, it is possible to conclude that reaction II is not a plausible mechanism for the scavenging of the studied free radicals because CARs are worse electron acceptors but better electron donors than the free radicals are. In a previous work,[11] we also suggested that the capacity to accept electrons prevents oxidative stress because electron acceptors can inhibit the formation of superoxide anion ($O_2^-\bullet$), a very damaging oxygen species that contributes to oxidative stress. The electron-acceptor molecules could prevent oxidative stress with the capture of this free radical. The possibility that CARs can prevent oxidative stress by trapping or deactivating the superoxide anion is still an open question.

Chemical Reactivity Theory for ET Reactions. Even though the full-electron transferability index ($\Delta\Theta$) was shown to properly describe the viability of ET processes, it was obtained empirically. However, ET reactions can be rationalized within chemical reactivity theory (CRT).[20] In general, reaction I can be rewritten for any electron donor (d) reacting with any electron acceptor (a) as

$$d + a \rightarrow d^+ + a^-$$
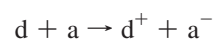
The energy difference for this reaction is given by

$$\Delta E = E_{d^+} + E_{a^-} - E_d - E_a \tag{8}$$

where

$$E_{d^+} = E_d(N_d^0 - 1) \tag{9}$$

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and

$$E_{a^-} = E_a(N_a^0 + 1) \qquad (10)$$

Using a Taylor expansion of the energy in powers of the number of electrons (N), one obtains

$$E(N) = E(N^0) + \left(\frac{\partial E}{\partial N}\right)_v \Delta N + \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_v \Delta N^2 \qquad (11)$$

where the first derivative at fixed external potential, v, is equal to the chemical potential or the negative of the electronegativity

$$\mu = \left(\frac{\partial E}{\partial N}\right)_v = -\chi \qquad (12)$$

and the second derivative of the energy is associated with the hardness

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_v \qquad (13)$$

If the number of electrons transferred in this reaction is unity (i.e., $\Delta N = \pm 1$), then it is possible to write the following expressions for the energies of the donor and acceptor

$$E_d(N_d^0 - 1) - E_d(N_d^0) = -\mu_d + \frac{1}{2}\eta_d = E_d + \chi_d + \frac{1}{2}\eta_d \qquad (14)$$

and

$$E_a(N_a^0 + 1) - E_a(N_a^0) = \mu_a + \frac{1}{2}\eta_a = E_a - \chi_a + \frac{1}{2}\eta_a \qquad (15)$$

Adding eqs 14 and 15, one recovers ΔE from eq 8 by using eqs 9 and 10; then

$$\Delta E = \chi_d - \chi_a + \frac{1}{2}(\eta_d + \eta_a) \qquad (16)$$

This equation indicates that the energy index that measures the full ET process is the electronegativity difference plus the arithmetic mean of the hardness values. To explore the validity of this approximation, a plot of the adiabatic Gibbs free energies versus ΔE of eq 16 is presented in Figure 8. As can be seen, the calculated free energies show a good correlation with the energy difference of eq 16.

Comparing eq 7 with eq 16, it is possible to conclude that the full-electron transferability index proposed previously is not theoretically justified within the CRT. However, both $\Delta\Theta$ and ΔE are in good agreement with the predictions obtained from ΔG.

Concluding Remarks

The first conclusion that we can drawn from this work is that the electron affinity of free radicals is very important for ET reactions and that, for exergonic reactions (involving the
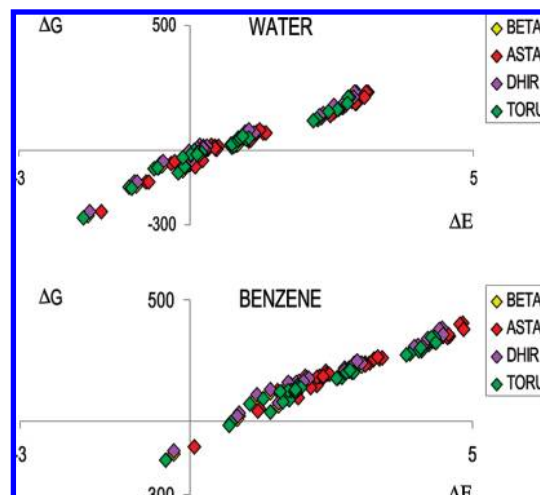

Figure 8. ΔG at 298 K for reaction I in water and benzene, as a function of ΔE from eq 16.

radical scavengers studied here), the limiting value of the electron affinity of free radicals is close to 5 eV.

The second conclusion refers to the two indexes $\Delta\Theta$ and ΔE (eqs 7 and 16, respectively). Both agree well with ΔG; this is very interesting because one is empirical and the other is derived from the CRT and both indicate that the reaction will be favored as the electron affinity of the radical becomes larger, but clearly, the viability of the reaction should depend on the properties of both the radical and the radical scavenger.

The FEDAM provides a first approach to the studied phenomena, and qualitative information can be derived from it. If the free radicals are located to the left of the CARs in the FEDAM, then the ET transfer is predicted to be nonfeasible. If the radicals are located to the right of the CARs in the map, then the information that can be obtained from the FEDAM is less straightforward. This is not a sufficient condition for the reaction to be exergonic because a significant separation is also needed. According to our results, it seems that, if this separation is larger than 0.2 and 0.4 eV in polar and nonpolar environments, respectively, then, the reaction is predicted to be exergonic. For more precise information, the FEDAM is not sufficient, and thermodynamic data need to be calculated.

Radical scavengers prevent radical damage, either by oxidation or by reduction of free radicals, but in the case of CARs and the free radicals considered in this study, oxidation is not a plausible mechanism. To understand the real value of CARs as protective radical scavengers, it is important to fully comprehend the chemistry of these molecules. To this end, more studies concerning the reactions of peroxide radicals with several CARs are in progress.

Supporting Information Available: FEDAM in the gas phase. Gibbs free energies of reaction in the gas phase. Vertical and adiabatic IEs and EAs for the reacting species in benzene and water solution. Optimized geometries, energies, and S2 values of reacting species. This material is available free of charge via Internet at http://pubs.acs.org.

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