Donator Acceptor Map for Carotenoids, Melatonin and Vitamins

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Bright yellow and red colors in animals and plants are assumed to be caused by carotenoids (CAR). In animals, these pigments are deposited in scales, skin and feathers. Together with other naturally occurring and colorless substances such as melatonin and vitamins, they are considered antioxidants due to their free-radical-scavenging properties. However, it would be better to refer to them as "antiradicals", an action that can take place either donating or accepting electrons. In this work we present quantum chemical calculations for several CAR and some colorless antioxidants, such as melatonin and vitamins A, C and E. The antiradical capacity of these substances is determined using vertical ionization energy (I), electron affinity (A), the electrodonating power (ω^-) and the electroaccepting power (ω^+). Using fluor and sodium as references, electron acceptance (R_a) and electron donation (R_d) indexes are defined. A plot of R_d vs R_a provides a donator acceptor map (DAM) useful to classify any substance regarding its electron donating−accepting capability. Using this DAM, a qualitative comparison among all the studied compounds is presented. According to R_d values, vitamin E is the most effective antiradical in terms of its electron donor capacity, while the most effective antiradical in terms of its electron acceptor capacity, R_a, is astaxanthin, the reddest CAR. These results may be helpful for understanding the role played by naturally occurring pigments, acting as radical scavengers either donating or accepting electrons.

Introduction

Bright yellow and red colors in animals are thought to be caused by a number of carotenoids (CAR) deposited in scales, skin and feathers.[1−6] It has been claimed that CAR are responsible for much of the yellow, orange and red pigmentation manifested in the animal kingdom, and many articles have been written (reviewed in refs 3 and 4), affirming the idea that CAR consist of pigments and antioxidants. For many years, the idea has existed that the pigmentation in animals may indicate antioxidant status, given that these substances have antioxidant properties.[7,8] Animals may face a tradeoff when allocating CAR (acquired from the diet) either for physiological or for coloration purposes. It is assumed that higher-quality individuals (those who acquire more carotenoids or are in better state of health) are able to devote more of the acquired CAR to coloration, which in turn appears to be important for sexual advertisement and ultimately reproduction and species survival. Coloration thus reveals individual quality and becomes the target of sexual selection. Of course, colorless antioxidant substances, such as vitamins and melatonin, are also present in animals and plants. Antioxidants are important since these molecules scavenge free radicals, thus limiting cellular damage.

Several studies exist which discuss CAR and vitamins[7−35] as antioxidants. There are three mechanisms that are discussed in the literature[7−20] for the reaction of free radicals with CAR, namely, electron transfer reaction, hydrogen atom transfer from the CAR, and radical addition to the CAR. Concerning the first mechanism, it was reported that, in order to scavenge free radicals, CAR can either donate or accept unpaired electrons.[7−17] Antioxidant molecules become oxidized by transferring electrons to the free radical, a reaction that prevents other molecules undergoing oxidation reactions with this free radical. As this reaction halts oxidation, these molecules are labeled as antioxidants. On the other hand, when CAR accepts an unpaired electron from the free radical, the free radical loses electrons and therefore becomes oxidized and CAR molecules are reduced. This charge transfer does not prevent the oxidation of other molecules; it prevents the reduction of other molecules. In the literature, these substances are often referred to as antioxidants. However, as the relevant event in biological systems is the trapping of free radicals, it would be more precise to refer to these substances as "antiradicals". Antioxidation and antireduction represent two sides of the same coin: antiradical activity through electron transfer. Antiradical action prevents radical damage, either by the oxidation or by the reduction of free radicals. Hence, antiradical substances can be classified in terms of their oxidation and reduction potential.

In order to evaluate oxidation potential, it has been demonstrated[9]that relative antioxidant efficiency is determined by vertical ionization energy (I). Compounds that have low I values are the most easily oxidized substances, and as a result,

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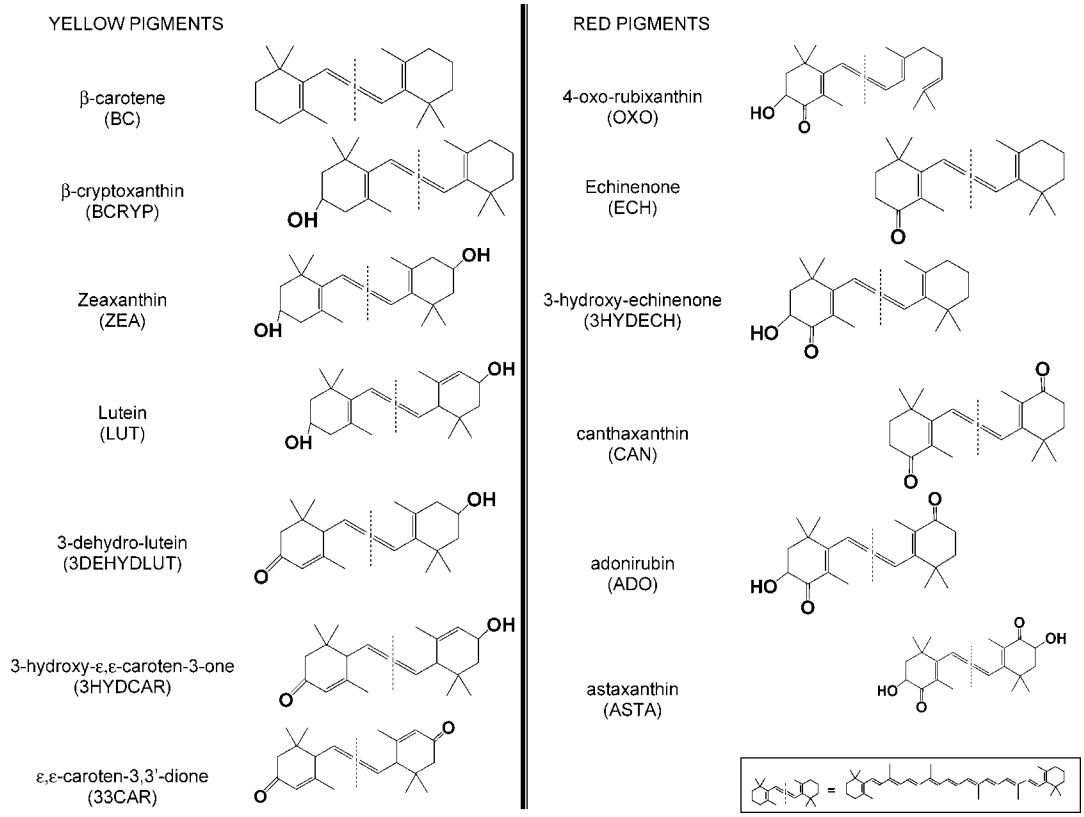

Figure 1. Carotenoid pigments. Schematic representation of the molecular structure of thirteen carotenoid pigments found in the feathers of the male house finch.[4]

they represent the most efficient antiradicals, in terms of their electron donating capability. In order to evaluate reduction potential, it is necessary to estimate the potential for electron acceptance. This can be achieved by assessing vertical electron affinity (A), which is a good indicator of the electron attraction force. Substances with high and positive A values have a greater capacity for accepting electrons. Compounds that have large positive A values are the most easily reduced substances, and thus they represent the most efficient antiradicals, expressed in terms of their electron accepting capability. Another useful measure of electrodonating and electroaccepting power has been reported recently by Gázquez et al.[36] They established a simple charge-transfer model and analyzed the global response of a molecule immersed in an idealized environment that may either withdraw or donate charge. A quadratic interpolation for the energy as a function of the number of electrons was proposed to evaluate the response of a molecule to charge acceptance or withdrawal in terms of the electron affinity and the ionization potential. Within this approximation, these authors conclude that the propensity to donate charge, or electrodonating power, may be defined as

$$\omega^- = \frac{(3I + A)^2}{16(I - A)} \quad (1)$$

whereas the propensity to accept charge, or electroaccepting power, may be defined as

$$\omega^+ = \frac{(I + 3A)^2}{16(I - A)} \quad (2)$$

In the case of electrodonating power, lower values imply a greater capacity for donating charge. In the case of electroaccepting power, higher values imply a greater capacity for accepting charge. It is important to note that I and A refer to donating or accepting one electron, while ω^- and ω^+ refer to fractional charges. In this way, the electrodonating and electroaccepting powers are based on a simple charge transfer model expressed in terms of the chemical potential and the hardness. The chemical potential measures the charge flow direction together with the capacity to donate or accept charge, providing for the charge donation process more emphasis to the ionization potential than to the electron affinity. Contrary, the electroaccepting power gives more significance to the electron affinity than to the ionization potential and hardness measures the resistance to the flow of the electrons.

As it is necessary for substances to donate or accept unpaired electrons in order to trap free radicals, it is possible to use ω^- and ω^+ to analyze the antiradical capacity of pigments and other well-known antioxidant substances. In this article, we report quantum chemical calculations for several CAR and certain colorless antioxidants such as melatonin, vitamins A, C and E for this purpose. The antiradical capacity of CAR, melatonin, vitamin A, C and E is analyzed using I, A, ω^- and ω^+. Using fluor and sodium as references, electron acceptance (R_a) and electron donation (R_d) indexes are defined, producing a donator acceptor map (DAM) useful to classify any substance regarding its electron donating−accepting capability.

Computational Details

Density functional theory[37−39] as implemented in *Gaussian 03*[40] was used for all the calculations. Becke's 1988 functional, which includes the Slater exchange along with corrections involving the gradient of the density[41] and Perdew and Wang's 1991 gradient-corrected correlation functional[42] were employed in the calculations for complete optimizations, without symmetry constraints. D5DV basis sets were also employed.[43−45] Harmonic frequency analyses permitted us to verify optimized minima.

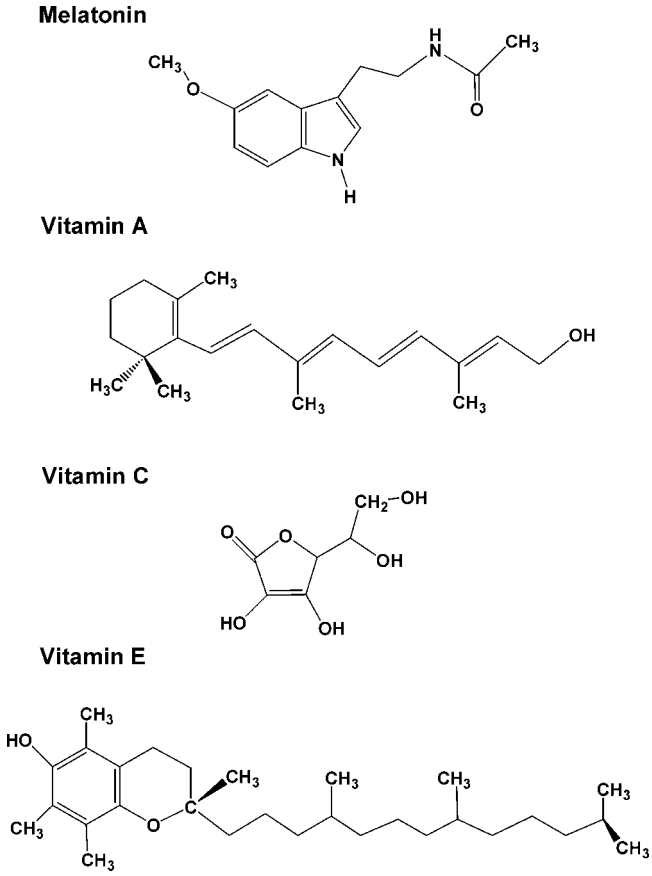

Figure 2. Melatonin and vitamins A, C and E. Schematic representation of the molecular structure of melatonin and vitamins A, C and E.

In order to compute *I* and *A*, further single-point calculations were necessary. *I* is calculated as the difference between the energy of the cation and the neutral molecule, assuming that both of these have the ground-state nuclear configuration of the neutral molecule. *A* is also calculated as vertical, and represents the energy difference between the neutral and the anion, calculated with the ground-state nuclear configuration of the neutral molecule. Solvent effects were included by using the polarizable continuum model (PCM),[46,47] with water and benzene as the solvents for polar and nonpolar environments, respectively.

The methodology used in this work was validated comparing the results with those obtained using B3LYP and 6-311G(d,p), as well as those reported previously by Galano.[9] The relative values for *I* and *A* do not depend on the functional and/or on the basis set.

Results and Discussion

In Figures 1 and 2 we schematically present the chemical structure of CAR, melatonin and vitamins A, C and E. CAR in Figure 1 identified in the house finch (*Carpodacus mexicanus*), a species which provides an apt model because male house finches have carotenoid-based plumage coloration in various parts of the body (head, underside and rump).[4] Coloration may vary from pale yellow to bright red, and this trait is crucial in the choice of mate, as females prefer to mate with males displaying the reddest and most saturated plumage coloration.[4] There are at least 13 different types of CAR (see Figure 1) found in the feathers of house finches, some of which typically confer a red hue and others which are yellow in color.[4] The pigments

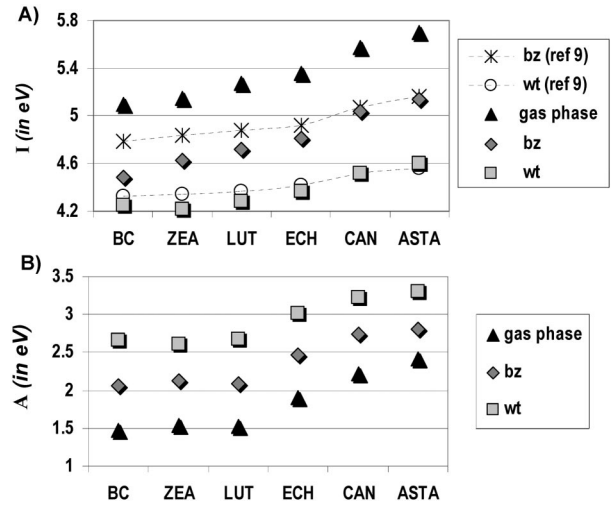

Figure 3. *I* and *A* values (in eV) for six selected CAR. (A) To calculate *I*, in a previous work,[9] full geometry optimizations were done using B3LYP/6-31G(d,p). Polar (water (wt)) and nonpolar (benzene (bz)) solvent effects were included by using the polarizable continuum model. In this work, full geometry optimizations using BPW91/D95V basis set were carried out. We also considered solvent effects for the same six CAR. Our results for the gas phase and those using benzene and water are largely consistent. The relative order is the same using various solvents and in the gas phase. (B) *A* values (in eV) for selected CAR, obtained in the gas phase, and using water (wt) and benzene (bz). Results in the gas phase are consistent with those using benzene and water.

are classified[48] as "yellow" when they present multipeaked spectral absorbance curves with $\lambda_{max} < 460$ nm. They are "red" when the shape of spectral absorbance represents a smooth curve as in $\lambda_{max} > 460$ nm. Previously Galano[9] reported *I* values for six of these CAR. She used a similar methodology, including solvent effects (water and benzene). A comparison between the results of Galano and those obtained in this work is presented in Figure 3. It is evident that our results are consistent with those presented in ref 9. Moreover, we performed single point energy calculations for the optimized structures of certain CAR and vitamins, considering solvent effects. As indicated in Figure 3, the results are largely consistent, so we may conclude that the effect of the solvent is not important when we want to obtain relative values for *I*. Also in Figure 3 we present *A* values, obtained for the gas phase as well as with benzene and water. The results are in agreement, and we can also conclude that the effect of the solvent is not important for the relative values of *A*.

Vertical Ionization Energy and Electron Affinity. Table 1 reports *I* and *A*, for CAR, vitamins and melatonin. The lowest *I* value is for BC and BRYP, and the highest corresponds to vitamin C. The low *I* values represent the most easily oxidized substances and indicate the most efficient antiradicals, expressed as their electron donating capability. Generally, *I* values from Table 1 indicate that yellow CAR act as better antioxidant molecules than red ones, while melatonin and vitamins are the poorest antioxidant molecules. According to these results, melatonin and vitamins are not as good antioxidants as CAR. As shown in Table 1, *A* is both large and positive in the case of all animal pigments (CAR) and is negative in the case of melatonin and vitamins C and E. For vitamin A, the value is positive but lower than the values are for pigments. One important conclusion that we can derive from these results is that naturally occurring pigments are able to accept an electron. *A* is positive, which means that the anion is more stable than the neutral molecule, i.e. they are more capable of accepting

TABLE 1: Vertical Ionization Energies (I), Vertical Electron Affinities (A)[a], Electron Donation and Acceptance Powers (ω^- and ω^+) and Indexes (R_d and R_a), Obtained with Eqs 1−4[b]

	I (eV)	A (eV)	ω^- (donating power)	ω^+ (accepting power)	R_d	R_a
Na	5.14	0.54	3.46	0.62	1.00	0.18
F	17.54	3.40	13.80	3.40	3.99	1.00
			Yellow			
BC	5.1	1.47	4.84	1.56	1.40	0.46
BCRYP	5.09	1.52	4.94	1.63	1.43	0.48
ZEA	5.15	1.54	5.00	1.65	1.44	0.49
LUT	5.27	1.52	5.01	1.61	1.45	0.47
3DEHYLUT	5.41	1.72	5.46	1.89	1.58	0.56
3HYDCAR	5.52	1.63	5.32	1.74	1.54	0.51
33CAR	5.59	1.75	5.58	1.91	1.61	0.56
			Red			
OXO	5.21	1.98	6.00	2.41	1.73	0.71
ECH	5.36	1.9	5.84	2.21	1.69	0.65
3HYDECH	5.35	1.97	6.00	2.34	1.73	0.69
CAN	5.57	2.22	6.69	2.79	1.93	0.82
ADO	5.69	2.36	7.09	3.06	2.05	0.90
ASTA	5.7	2.42	7.26	3.20	2.10	0.94
			Colorless			
vitamin E	6.70	−5.55	1.08	0.51	0.31	0.15
melatonin	6.83	−1.00	3.03	0.12	0.88	0.03
vitamin C	8.53	−0.39	4.46	0.38	1.29	0.11
vitamin A	6.22	0.54	4.06	0.68	1.17	0.20

[a] I and A values were obtained according to $CAR \rightarrow CAR^+ + 1e$ [$I = E(CAR^+) - E(CAR)$]; $CAR^- \rightarrow CAR + 1e$ [$A = E(CAR) - E(CAR^-)$]. For F and Na, experimental values of I and A are used. [b] Complete optimizations without symmetry constrains were done at the BPW91/D95V level. Reference values for well known oxidant (fluor) and reductant (sodium) are also shown.

electrons and thus they represent the most efficient antiradicals (expressed as their electron accepting capability). Melatonin and vitamins C and E have negative A values. This implies that these molecules will not accept an electron, i.e. it is necessary to give some energy in order to form the anion. These molecules are the most inefficient antiradicals (expressed as their electron accepting capability). As in order to trap free radicals, substances must either donate or accept electrons, animal pigments (CAR) are better antiradicals than melatonin and vitamins. They have lower I values than colorless substances (meaning that they are better antioxidants), and also they are able to act as antireductants without losing energy.

Electrodonating and Electroaccepting Power. The propensity to accept or donate charge can be analyzed using ω^- and ω^+ expressed in eqs 1 and 2. Results are presented in Table 1. In the case of electrodonating power (ω^-) low values imply strong capability to donate electrons. In the case of electroaccepting power (ω^+) high values imply strong capability to accept electrons. For CAR, high values for I also imply high values for ω^-. However, this is not the case for melatonin and vitamins because the ω^- value is lower for these substances than it is in the case of animal pigments, in contrast to I values. Apparently ω^- is a better indicator of antioxidant power than I, as it has been claimed that vitamins represent effective antioxidant substances. For example, there are reports that point to vitamin E as representing the most important lipid-soluble antioxidant present in cell membranes.[49] The electrodonating power of melatonin and vitamins is higher than that of animal pigments. According to these results, the order of reactivity expressed in terms of facility for oxidation, referring to the ω^- value, is as follows:

$$\text{colorless} > \text{yellow} > \text{red}$$

i.e. colorless antioxidants represent better electron donors than colored ones, with vitamin E representing the best antioxidant. Similarly, yellow pigments represent better antioxidants than red ones and the reddest pigment (ASTA) represents the worst antioxidant. Thus, these results might indicate that in animals, pigmentation is not a sign of antioxidant status. However, it is important to analyze the other side of the coin, in order to determine whether the color in animals may be an indication of their antiradical status. For this purpose, it is necessary to analyze A and ω^+. In Table 1 it is possible to appreciate that ω^+ correlates well with A. CAR are good "antireductants", and the reactivity order, in terms of facility for reduction considering A and ω^+ values, is as follows:

$$\text{red} > \text{yellow} > \text{colorless}$$

i.e. red pigments are better electron acceptors than yellow or colorless substances. ASTA is the best antireductant while melatonin is the worst. Moreover, red pigments are better antireductants than yellow ones, and the reddest pigment (ASTA) is the best antiradical (considering electron capture). Thus, both ω^- and ω^+ results appear to indicate that, among animals, pigmentation is not an indication of antioxidant status but rather an indication of antiradical status. These results suggest that it is important to analyze the charge flow direction together with the capacity to donate or accept charge. In order to have a complete description of the charge transfer process it is critical to consider I and A together, as Gázquez et al.[43] suggested for the electrodonating and electroaccepting power indexes.

In order to analyze solvent effects, I, A, ω^- and ω^+ were obtained in water and benzene for the six CAR shown in Figure 3 and also for vitamins E and C. Solvent effects increase the values with respect to those in the gas phase, but the general pattern is preserved. Hence, the above reached conclusions are qualitatively the same when a solvent is taken into account.

Donator Acceptor Map (DAM). In order to make a comparison with other well-known antioxidant and antireductant substances, experimental values of I and A for F and Na atoms were applied to obtain the corresponding ω^+ and ω^- values. F represents a good electron acceptor while Na represents a good electron donor. For any substance L, we define an electron acceptance index as

$$R_a = \frac{\omega_L^+}{\omega_F^+} \tag{3}$$

If $R_a = 1$, then $\omega_L^+ \cong \omega_F^+$ and L is as good an electron acceptor as F. If $R_a > 1$, then $\omega_L^+ > \omega_F^+$ and L is a better electron acceptor than F. If $R_a < 1$, then $\omega_L^+ < \omega_F^+$ and L is a worse electron acceptor than F. In the same way, the electron donation index is defined as

$$R_d = \frac{\omega_L^-}{\omega_{Na}^-} \tag{4}$$

If $R_d = 1$, then $\omega_L^- \cong \omega_{Na}^-$ and L is as good an electron donor as Na. If $R_d > 1$, then $\omega_L^- > \omega_{Na}^-$ and L is a worse electron donor than Na. If $R_d < 1$, then $\omega_L^- < \omega_{Na}^-$ and L is a better electron donor than Na.

Figure 4 shows schematically a plot of R_d vs R_a providing a donator acceptor map (DAM). There are four regions in the DAM, namely: (1) the *best antiradical* zone where L is a good electron donor (R_d small) and a good electron acceptor (R_a

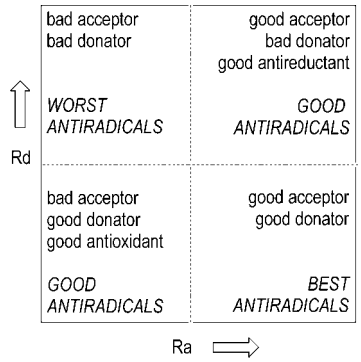

Figure 4. Donator acceptor map (DAM). Four regions are distinguished as described in detail in the text. Dash lines separating regions are only indicative, to aid visualization.

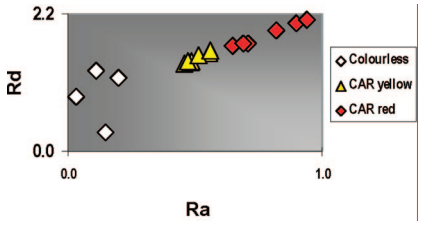

Figure 5. DAM for red and yellow CAR, melatonin, vitamins A, C and E.

large); (2) the *worst antiradical* region where L is a bad electron donor (R_d large) and a bad electron acceptor (R_a small); (3) the *good antireductant* sector (R_a and R_d large) where L is a good electron acceptor and hence a good antiradical; and (4) the *good antioxidant* region (R_a and R_d small) where L is a good electron donor and hence also a good antiradical. Note that three of the four zones in the DAM correspond to good antiradical substances. Using the DAM, any substance L can be classified in terms of its electron donating−accepting capability (respect to F and Na). As such, the DAM is a useful tool for a qualitative comparison among substances.

In Table 1, R_a and R_d for CAR, vitamins and melatonin are presented. Figure 5 shows the DAM for CAR, melatonin and vitamins. Results indicate that there are no better electron acceptors than F, but R_a values for ASTA and ADO are very close to 1. Only two substances, vitamin E and melatonin, are better electron donors than Na ($R_d < 1$). The DAM for the studied substances (see Figure 5) shows that CAR are in the good antireductant zone while the colorless compounds belong to the good antioxidant sector. ASTA is the best electron acceptor among all studied substances. In living organisms, red CAR pigments might act as antireductants and, as such, as antiradicals. Yellow CAR are closer to the worst antiradical section than the red CAR. As antiradicals, they are certainly less effective. Vitamin E is the best antioxidant and as such a good antiradical, while vitamin C is the worst. CAR are good antiradicals because they are good antireductants, i.e. yellow and red CAR are able to neutralize free radicals by accepting electrons. Melatonin and vitamins E and A are able to scavenge free radicals more efficiently than CAR, mainly by donating electrons, but the capacity of these substances for accepting electrons is very low.

Conclusions

It is possible to determine the antiradical capacity of CAR, melatonin, and vitamins C and E using I, A, ω^-, ω^+, R_a and R_d. I, ω^- and R_d refer to the electron donor capacity. Apparently ω^- is a better indicator of antioxidant power than I. A, ω^+ and R_a refer to the electron acceptor capacity. According to these results, vitamin E is the best antiradical substance acting as an antioxidant, while the best antiradical acting as an antireductant is ASTA, the reddest CAR. Vitamin C is classified as not as good an antiradical substance as either CAR or vitamin E. Using the DAM, any substance L can be classified in terms of its electron donating−accepting capability (with respect to F and Na). As such, the DAM permits a straightforward qualitative comparison among substances. Overall, our results show that it is misleading to equate the radical scavenging function of substances with their oxidation potential. We must consider also their antireductant potential. The possibility of either accepting or donating electrons must be important for the charge transfer process, which is highly relevant for the metabolism of living organisms. These results may be useful for interpreting the role played by animal pigments as radical scavengers, either donating or accepting electrons.

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