

Antiradical capacity of ommochromes

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Received: 23 November 2014 / Accepted: 20 July 2015 / Published online: 4 August 2015
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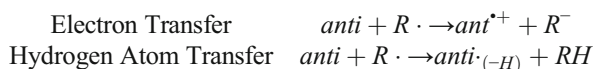
Abstract Ommochromes are colored substances that apparently function as biological signals among arthropods and insects. These substances may prevent oxidative stress by scavenging free radicals. Two principal mechanisms exist for scavenging free radicals: the electron transfer and hydrogen atom transfer. In this investigation, a theoretical study of the antiradical capacity of five ommochromes was performed within the density functional theory framework. Vertical ionization energy and vertical electron affinity were used to study the electron transfer mechanism between ommochromes and four free radicals: $\text{CH}_3\text{O}\cdot$, $\text{NO}_2\cdot$, $\text{HO}\cdot$, and $\text{HOO}\cdot$. For the hydrogen transfer mechanism, dissociation energy (D_0) and Gibbs free energy were calculated, taking into account hydrogen atoms at different positions in the ommochromes. Both mechanisms are thermodynamically possible. The best antiradical is ommatin D. The UV/VIS spectra for ommochromes were obtained with ommatin D registering as the ommochrome with the

greatest λ_{max} value. In summary, ommatin D is the best antiradical and also the redder molecule. These results are important and may help to elucidate the function of these molecules in the animal kingdom.

Keywords Biological pigments · Antioxidants · DFT calculations · Donor acceptor map

Introduction

Free radicals present one or more unpaired electrons. Usually these are unstable and very reactive with other chemical species. The presence of free radicals causes what is known as oxidative stress, implicated in the development of a large number of health disorders [1–9]. Antiradicals are chemical compounds that are able to scavenge free radicals and therefore contribute to the control of oxidative stress. Oxidative stress occurs when the number of free radicals exceeds antiradicals. Two possible mechanisms exist for scavenging free radicals; the electron transfer and the hydrogen atom transfer [10]. These mechanisms can be represented as follows:



In these representations, *anti* is any antiradical molecule, $R\cdot$ is the free radical, and $\textit{anti}_{(-H)}\cdot$ is the dehydrogenated antiradical molecule.

There are many molecules in nature that act as effective antiradicals [11–17]. These can be either colorless or colored. Carotenoids and psittacofulvins comprise red and yellow substances and an example of these colored antiradicals are found in the feathers of birds. Likewise, ommochromes are colored substances that may act as

Electronic supplementary material The online version of this article (doi:10.1007/s00894-015-2773-3) contains supplementary material, which is available to authorized users.

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biological signals among arthropods and insects [18, 19]. Experimental results show that ommochromes exhibit redox properties, enabling them to be either electron-donors or electron-acceptors [20, 21]. Apparently, these substances protect the bodies of insects against UV photodestruction.

Kynurenine, kynurenic acid, 3-hydroxykynurenine, xanthommatin, and ommatin D are all ommochromes. They are the main products of the metabolic pathway of tryptophan in invertebrates [22]. Previous results indicate that kynurenine, kynurenic acid, and 3-hydroxykynurenine present antioxidant properties, however other reports classify 3-hydroxykynurenine and kynurenic acid as able to induce oxidative damage [20, 21]. This has been associated with a number of neurological and psychiatric disorders [23–25]. The oxidative damage produced by ommochromes is related to the imbalance between neuroprotective and neurodegenerative metabolites in the kynurenine pathway.

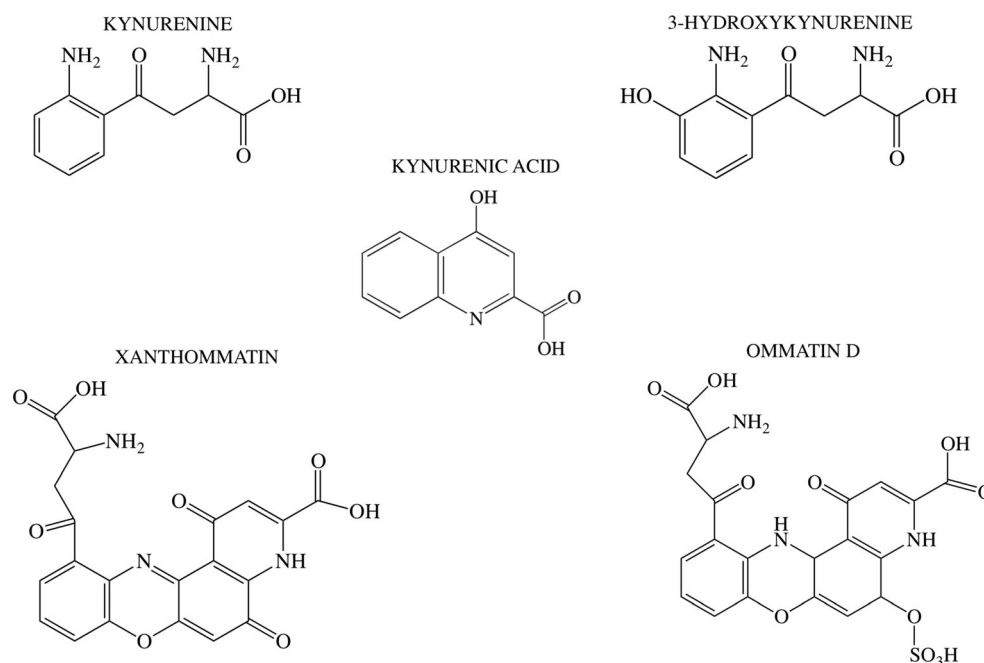
Results reported in the literature that refer to the antiradical properties of certain ommochromes are all experimental [20, 21, 23, 26]. In order to elucidate the possible mechanisms and reactivity of these molecules, it is important to also investigate these ommochromes from a theoretical point of view. For this reason, we present a theoretical study of the scavenge free radical capacity of five ommochromes (Fig. 1). Two possible reaction mechanisms, electron transfer and hydrogen atom transfer, are analyzed. The antiradical capacity of ommochromes is compared to previous results for carotenoids [11, 12, 15, 16]. To compare with the experimental values [18, 26] the UV/VIS spectra of neutral ommochromes are obtained, assuming that water is the solvent.

Computational details

Different conformers of ommochromes were generated using a systematic search with a force field MMFF94 [27–31]. One hundred forty conformers for kynurenine and 3-hydroxykynurenine, 70 for xanthommatin and ommatin D, and seven for kynurenic acid were used as initial geometries that were fully optimized at density functional theory level. Calculations related to geometries optimization and antiradical analysis of ommochromes were undertaken using Gaussian 09 implementation [32]. The geometries of all conformers were fully optimized at B3LYP/6-311G+(d,p) level of theory [33–35]. In order to verify optimized minima, harmonic analyses were performed and local minima were identified (zero imaginary frequencies). Since the geometries of all the conformers were fully optimized, we are confident that the reported results represent global minimum. The most stable conformers are included in Tables S1 to S5. As can be seen, there are five conformers with similar stability. All these structures could be present in an experiment. The conclusions of this investigation will be the same for these conformers and for this reason in what follows we will present only results for the most stable structures.

Two mechanisms to prevent oxidative stress were analyzed for the most stable conformers. To investigate the electron transfer mechanism, calculations have been carried out using the B3LYP hybrid HF-density functional and the 6-311+G(d,p) basis set. Vertical ionization energy (IE) and vertical electron affinity (EA) were obtained from single point calculations of cationic and anionic molecules, using the optimized structure of the neutrals.

Fig. 1 Structural formula of ommochromes under study



Since the implicit consideration of the medium does not represent significant differences in the optimized structures (see Table S6 of Supplementary material), solvent effects were included by single point calculations using SMD solvation model [36] with water to mimic polar environment. In order to analyze the effect of hydrogen bonds we also added water molecules explicitly. Table S7 reports the optimized structures with water molecules included. As expected, some bond distances are different due to the presence of the hydrogen bonds. However, with the values of IE and EA we arrive to the same conclusions for both systems (with and without molecules of water explicitly included) and therefore, we consider that the hydrogen bonds do not determine the antiradical properties of these compounds.

For the hydrogen atom transfer mechanism, the capacity of ommochrome to scavenge free radicals was analyzed through the dissociation energy of one hydrogen atom and using the Gibbs free energy for the hydrogen transfer reaction between ommochromes and four free radicals ($\text{CH}_3\text{O}\cdot$, $\text{NO}_2\cdot$, $\text{HO}\cdot$, and $\text{HOO}\cdot$). Free radicals considered in this study were selected to be representative for containing oxygen, carbon, and nitrogen atoms. The UV-visible spectra were computed with time-dependent density functional theory (TDDFT) at B3LYP/6-311G+(d,p) level of theory considering water as solvent.

Results and discussion

The optimized structures of the most stable conformers for each ommochrome in gas phase are reported in Fig. 2. Bond distances and angles are also included. All molecules present intramolecular hydrogen bonds (dot lines) that stabilize the structures. Kynurenic acid is the only molecule in Fig. 2 that is

planar. The other four molecules present a number of atoms out of the plane. Kynurenine and 3-hydroxykynurenine are very similar; structures differ in terms of the presence of a single OH that forms an extra hydrogen bond with the amino group.

Table 1 reports the UV-visible maxima absorption wavelength (λ_{max}) of ommochromes in water. Kinurenine and kynurenic acid present the smallest λ_{max} . The longest λ_{max} is for ommatin D, which is also the largest molecule. Apparently, as the size of the molecule increases the electrons become more delocalized, excitation energy decreases and consequently λ_{max} increases. The comparison of the theoretical results with available experimental values reported previously [18, 26] indicates that theory and experiment concur well. The calculated λ_{max} values are overestimated in comparison with the experimental data. The λ_{max} of kynurenine, kynurenic acid and 3-hydroxykynurenine are located within the ultraviolet region. Xanthommatin and ommatin D present λ_{max} in the visible violet-blue region of the spectrum. In spite of the differences in absolute values, experimental and theoretical data mainly conform, since values for λ_{calc} are located in the same region as λ_{exp} .

The capability to donate or accept electrons can be qualitatively studied with reference to a full-electron donor acceptor map (FEDAM), which is an effective representation for studying the antiradical capacity of any molecule. FEDAM was reported previously [12, 15] and is included in Fig. 3 to facilitate the discussion. Reduced IE values imply that the molecule is an effective electron donor. Large EA values indicate that the molecule is an effective electron acceptor. Molecules situated up to the right of FEDAM are effective electron acceptors. Those localized down to the left are effective electron donors. Electrons will be transferred from systems that are down to the left, to those situated up to the right. With completely different molecules, the comparison is also valid.

Fig. 2 Optimized structures of ommochromes. Distances (Å) and angles (°) are included

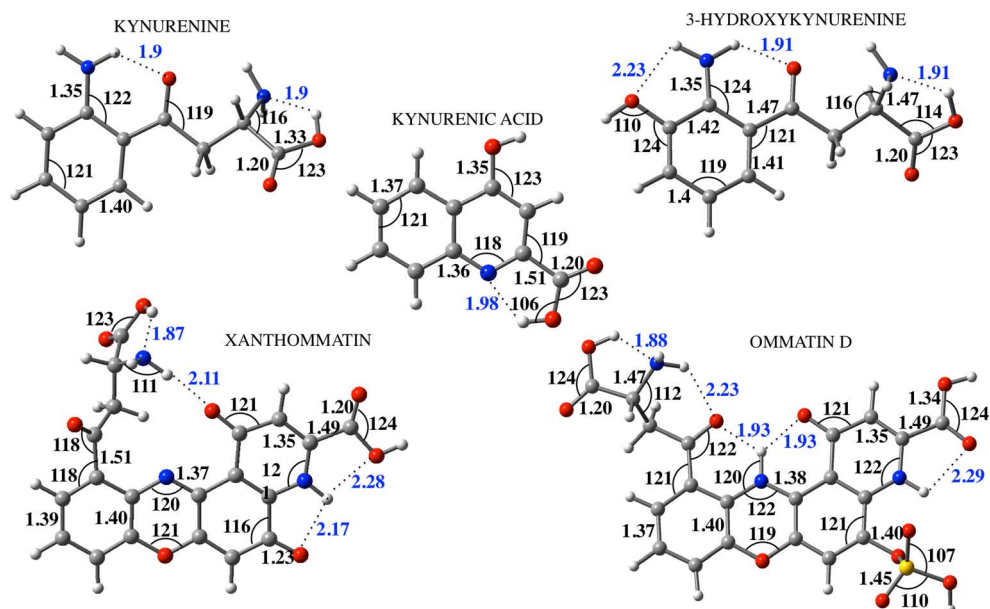


Table 1 Experimental and calculated data for the UV/VIS spectra of ommochromes

	Solvent = water			
	Experimental λ_{\max}	Calculated λ_{\max}	Oscillator strength	$\lambda_{\text{exp}} / \lambda_{\text{calc}}$
Kynurenine	363	248	0.01	1.46
Kynurenic acid	332	252	0.54	1.31
3-hydroxykynurenine	373	267	0.20	1.39
Xanthommatin	459	440	0.56	1.04
Ommatin D	486	474	0.20	1.02

In Fig. 3 we included β -carotene and astaxanthin that are very different molecules, in order to compare the antiradical capacity of these molecules with those for ommochromes.

Figure 3 presents the FEDAM for the systems being studied, with water as the solvent. As is evident, ommochromes are down to the left and will transfer electrons to free radicals that are up to the right.

It was previously reported [17] that the condition of $IE_d < EA_a$ must be fulfilled, in order to have an exergonic electron transfer reaction (IE_d indicates the vertical ionization energy of electron donor and EA_a indicates the vertical electron affinity of electron acceptor). The location in the FEDAM helps to determine which molecule is the electron donor and which the electron acceptor. Likewise, Fig. 3 indicates that ommochromes will always be the electron donors and free radicals the electron acceptors. Table 2 presents the values of IE and EA for ommochromes and free radicals in water. $IE_d < EA_a$ only in the case of kynurenine, 3-hydroxykynurenine, and ommatin D, with $\text{HO}\cdot$ as the electron acceptor. This means that the electron transfer to $\text{HO}\cdot$ is exergonic only for kynurenine, 3-hydroxykynurenine, and ommatin D. Similarly, ommatin D is the molecule with the lowest EI value and

therefore the best electron donor. Consequently, it represents the best antiradical molecule among the ommochromes that were studied.

The results for some yellow and red carotenoids have been reported previously [11, 12, 16]. Carotenoids are colored substances present in nature that are good antiradicals. Since we also want to know if ommochromes are natural colored substances that are good antiradicals, it is useful to compare our results with the previous ones for carotenoids. We have repeated the calculations for β -carotene and astaxanthin, in order to make a direct comparison with the values of the ommochromes. For β -carotene and astaxanthin in water, the values are included in Fig. 3. At the B3LYP/6-311+G(d,p) level, IE for β -carotene and astaxanthin is equal to 4.35 and 4.64 eV, respectively. For ommochromes, the values of IE vary from 5.07 to 6.35 eV. As carotenoids are better electron donors than ommochromes (IE is smaller for carotenoids than for ommochromes), it is possible to conclude that carotenoids are better free radical scavengers than ommochromes, in terms of the electron transfer mechanism.

For the analysis of the hydrogen atom transfer mechanism, the bond dissociation energy D_0 was calculated considering

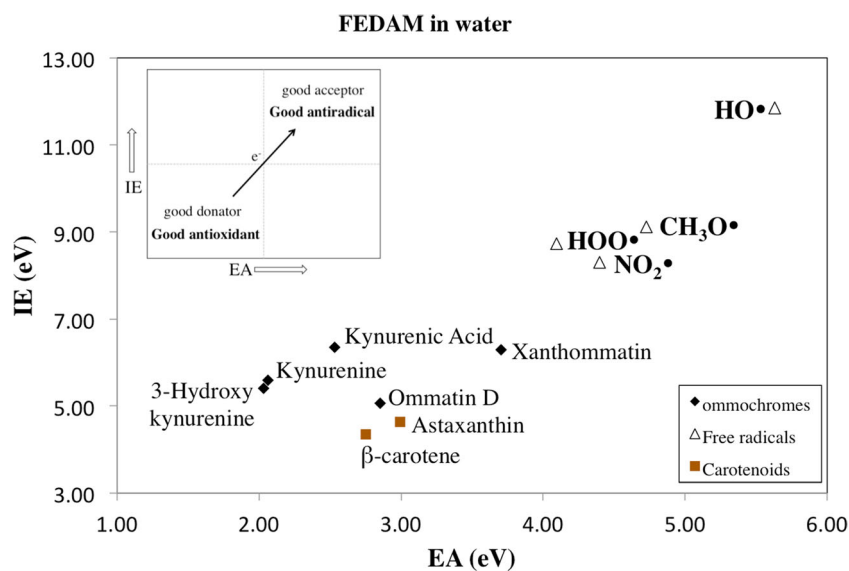
Fig. 3 FEDAM for ommochromes and free radicals considered in this study

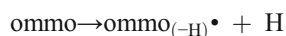
Table 2 Vertical ionization energy (IE) and electron affinity (EA) in eV and water was the solvent

Molecules	IE	EA
Kynurenine	5.60	2.06
Kynurenic acid	6.35	2.53
3-Hydroxykynurenine	5.41	2.03
Xanthommatin	6.30	3.70
Ommatin D	5.07	2.85
CH ₃ O•	9.12	4.73
NO ₂ •	8.30	4.40
HO•	11.85	5.63
HOO•	8.72	4.09

hydrogen atoms at different positions for ommochromes in gas phase. The dissociation energy was calculated as:

$$D_0 = \left[(E(H) + E(\text{ommo}_{(-H)})) \right] - [E(\text{ommo})]$$

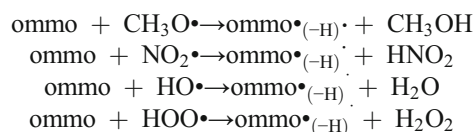
assuming the following reaction:



Ommochromes are represented as ommo and ommo•_(-H), corresponding to the dehydrogenated ommochromes. The dehydrogenated ommochromes were fully optimized (optimized structures are included in Figs. S1 to S5 of Supplementary material). To find out which of the ommochromes represented the most reactive antiradical, two aspects were considered: the number of reactive hydrogen atoms in the molecule and the Gibbs free energy for the hydrogen atom transfer, which was calculated considering four free radicals (CH₃O•, NO₂•, HO•, and HOO•). The hydrogen transfer reaction can be represented as follows:



The specific reactions considered, consisted of the following:



Negative values for Gibbs free energies (ΔG) indicate that the reaction is exergonic and energetically possible. For each ommochrome, the hydrogen atoms were dissociated from different atomic positions. The hydrogen atom for which dissociation produces exergonic reactions is considered as active hydrogen. Molecules with many active hydrogen atoms are more reactive than those with few active hydrogen atoms and will therefore act as better antiradicals.

The results of the bond dissociation energy D_0 and ΔG for the hydrogen atom transfer are reported in Tables 3, 4, 5, 6, and 7. Each hydrogen atom has been labeled in accordance with the scheme that is also included. It is well known that the C-H bond is weaker when the carbon atom has sp^3 hybridization. In agreement with this, all hydrogen atoms bonded to sp^2 carbon atoms have larger D_0 values than those bonded to sp^3 carbon atoms. The formation of hydrogen bonds stabilizes the molecule, and therefore the energy to dissociate an atom forming hydrogen bonds increases in comparison to those atoms that do not form hydrogen bonds.

In Table 3, results for kynurenine are presented. Hydrogen atoms bonded to sp^2 carbon atoms present the largest D_0 , whilst two hydrogen atoms bonded to sp^3 carbon atoms (atoms 8 and 9) present the lowest D_0 . The hydrogen atoms from the amino and hydroxyl groups (atoms 12 and 13) form hydrogen bonds and therefore D_0 is larger. For the reaction with free radicals, HO• is the most reactive, as it has negative ΔG values for the reaction with all hydrogen atoms of kynurenine. CH₃O• is also reactive but less so than HO•, as

Table 3 Structure and atom numbers of the hydrogen atoms that will be dissociated from kynurenine. Dissociation energies (D_0) of the corresponding hydrogen atom and Gibbs free energies (ΔG) considering four free radicals. All data are in eV

Atom number	D_0	ΔG			
		CH ₃ O•	NO ₂ •	HO•	HOO•
1	5.16	0.55	1.57	-0.17	1.25
2	5.08	0.47	1.48	-0.25	1.17
3	5.11	0.51	1.52	-0.21	1.21
15	4.41	-0.20	0.81	-0.92	0.50
6	5.00	0.36	1.38	-0.36	1.06
8	4.18	-0.46	0.56	-1.18	0.24
9	3.85	-0.79	0.23	-1.51	-0.09
13	4.56	-0.11	0.91	-0.83	0.59
12	4.86	0.18	1.20	-0.54	0.88

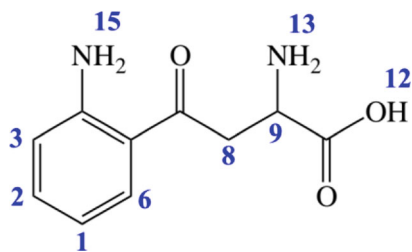
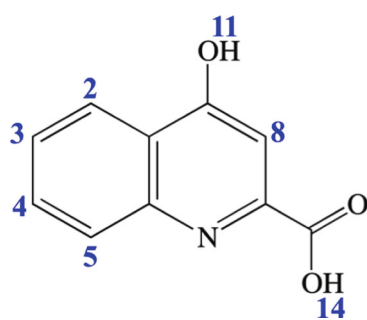


Table 4 Structure and atom numbers of the hydrogen atoms that will be dissociated from kynurenic acid. Dissociation energies (D_0) of the corresponding hydrogen atom and Gibbs free energies (ΔG) considering four free radicals. All data are in eV

Atom number	D_0	ΔG			
		$\text{CH}_3\text{O}\cdot$	$\text{NO}_2\cdot$	$\text{HO}\cdot$	$\text{HOO}\cdot$
2	5.13	0.53	1.54	-0.19	1.23
3	5.12	0.51	1.52	-0.21	1.21
4	5.10	0.49	1.51	-0.23	1.19
5	5.18	0.58	1.59	-0.14	1.28
11	4.05	-0.58	0.44	-1.29	0.12
8	5.23	0.63	1.65	-0.09	1.33
14	4.97	0.32	1.33	-0.40	1.02

there are only four hydrogen atoms of kynurenine with negative ΔG values. There is only one hydrogen atom in kynurenine that produces an exergonic reaction with $\text{HOO}\cdot$, which also corresponds to the lower value for D_0 (atom 9). The reaction with $\text{NO}_2\cdot$ is in all cases endergonic.

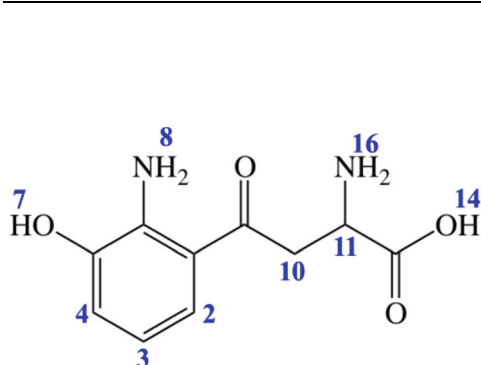
For kynurenic acid, results are reported in Table 4. All carbon atoms manifest sp^2 hybridization and therefore, the hydrogen atoms are tightly bound. The lowest D_0 corresponds to the hydrogen from a hydroxyl group (atom 11) that does not form hydrogen bonds. The negative values for ΔG indicate that all hydrogen atoms of kynurenic acid react with $\text{HO}\cdot$. For $\text{CH}_3\text{O}\cdot$, only the hydrogen atom of kynurenic acid with the lowest D_0 presents an exergonic reaction. For $\text{NO}_2\cdot$, and $\text{HOO}\cdot$, the free Gibbs energies indicate that all reactions are endergonic.

Table 5 presents the results for 3-hydroxykynurenine. The atom with lower dissociation energy corresponds to the hydroxyl group (atom 7). The hydrogen bonds between amino groups and oxygen (atoms 8, 16, and 14) increase the values for D_0 . As is the case for kynurenine, the 3-hydroxykynurenine reacts with $\text{CH}_3\text{O}\cdot$, $\text{HO}\cdot$, and $\text{HOO}\cdot$, although its reactivity is slightly greater because it presents more active hydrogen atoms than

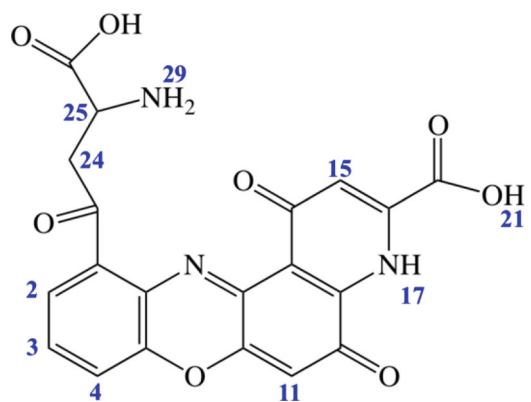
kynurenine and also because 3-hydroxykynurenine presents an exergonic reaction with $\text{NO}_2\cdot$. In fact, for all free radicals, the reaction with the hydrogen atom of the hydroxyl group (atom 7) of 3-hydroxykynurenine is exergonic.

Table 6 presents results for xanthommatin. The hydrogen atoms bonded to carbon atoms with sp^3 hybridization (atoms 24 and 25) have the lowest D_0 values. Atoms 17, 21, and 29 form hydrogen bonds and therefore the dissociation energy is larger. ΔG indicates that the hydrogen transfer reactions of xanthommatin with $\text{CH}_3\text{O}\cdot$, $\text{HO}\cdot$, and $\text{HOO}\cdot$ are exergonic. In the case of $\text{CH}_3\text{O}\cdot$, there are three possible hydrogen atoms of xanthommatin at three different atomic positions for which the hydrogen transfer mechanism is exergonic: two correspond to sp^3 carbon atoms and one to an amino group. Except for one sp^2 carbon atom (labeled with number 15), all the energies are exergonic for the reaction with $\text{HO}\cdot$. For $\text{HOO}\cdot$ there is only one exergonic reaction. In the case of the reaction with $\text{NO}_2\cdot$, all ΔG values are positive.

Table 7 presents the results for the hydrogen atom transfer mechanism with ommatin-D. As is evident, the lowest value for D_0 corresponds to NH (atom 17). This value is even lower than D_0 for hydrogen atoms located at sp^3 carbon atoms

Table 5 Structure and atom numbers of the hydrogen atoms that will be dissociated from 3-hydroxykynurenine. Dissociation energies (D_0) of the corresponding hydrogen atom and Gibbs free energies (ΔG) considering four free radicals. All data are in eV

Atom number	D_0	ΔG			
		$\text{CH}_3\text{O}\cdot$	$\text{NO}_2\cdot$	$\text{HO}\cdot$	$\text{HOO}\cdot$
2	5.04	0.40	1.42	-0.31	1.11
3	5.15	0.54	1.56	-0.17	1.24
4	5.09	0.49	1.51	-0.22	1.19
7	3.43	-1.13	-0.11	-1.85	-0.43
8	4.31	-0.27	0.74	-0.99	0.43
10	4.18	-0.46	0.56	-1.17	0.25
11	3.85	-0.78	0.24	-1.50	-0.08
16	4.56	-0.10	0.92	-0.82	0.60
14	4.86	0.18	1.20	-0.54	0.88

Table 6 Structure and atom numbers of the hydrogen atoms that will be dissociated from xanthommatin. Dissociation energies (D_0) of the corresponding hydrogen atom and Gibbs free energies (ΔG) considering four free radicals. All data are in eV


Atom number	D_0	ΔG			
		$\text{CH}_3\text{O}\cdot$	$\text{NO}_2\cdot$	$\text{HO}\cdot$	$\text{HOO}\cdot$
2	5.18	0.57	1.58	-0.15	1.27
3	5.13	0.52	1.53	-0.20	1.22
4	5.27	0.67	1.69	-0.05	1.37
11	5.27	0.67	1.69	-0.05	1.37
15	5.34	0.73	1.74	0.01	1.43
17	4.76	0.08	1.09	-0.64	0.78
21	4.95	0.31	1.32	-0.41	1.01
24	4.09	-0.51	0.50	-1.23	0.19
25	3.88	-0.76	0.36	-1.48	-0.06
29	4.68	-0.01	1.01	-0.72	0.69

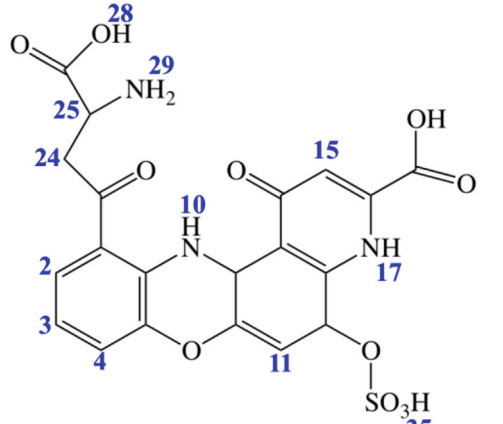
(atoms 24 and 25). As is the case for 3-hydroxykynurenine, ommatin-D presents negative ΔG values for the reaction with the four free radicals considered in this investigation. Moreover, ommatin-D is the ommochrome with the greatest amount of active hydrogen atoms.

According to the results already discussed, the best antiradical ommochrome considering the hydrogen atom transfer mechanism is ommatin-D, because it has the lowest value for D_0 (3.36 eV) and presents the greatest number of active hydrogen atoms. The worst antiradical is kynurenic acid. For all ommochromes, the most exergonic values for ΔG correspond to the atom with the lowest dissociation energy. Comparing these results with those obtained for β -carotene and astaxanthin, the lowest values of D_0 (obtained with the same

method and base used for ommochromes) are 3.12 eV for β -carotene and 3.24 eV for astaxanthin. Since these values are lower than the D_0 of ommochromes, we can conclude that carotenoids are better antiradicals than ommochromes.

Conclusions

Ommochromes are effective electron donors, although the electron transfer is energetically feasible only in the case of the reaction of $\text{HO}\cdot$ with kynurenine, 3-hydroxykynurenine, and ommatin D. Considering the electron transfer mechanism, ommatin-D is the best electron donor and therefore the best

Table 7 Structure and atom numbers of the hydrogen atoms that will be dissociated from ommatin-D. Dissociation energies (D_0) of the corresponding hydrogen atom and Gibbs free energies (ΔG) considering four free radicals. All data are in eV


Atom number	D_0	ΔG			
		$\text{CH}_3\text{O}\cdot$	$\text{NO}_2\cdot$	$\text{HO}\cdot$	$\text{HOO}\cdot$
2	5.03	0.41	1.43	-0.31	1.11
3	5.16	0.54	1.56	-0.17	1.24
4	5.19	0.58	1.60	-0.13	1.28
10	3.77	-0.81	0.20	-1.53	-0.11
11	5.29	0.65	1.66	-0.07	1.35
15	5.32	0.67	1.68	-0.05	1.37
17	3.36	-1.17	-0.16	-1.89	-0.47
24	4.13	-0.49	0.52	-1.21	0.21
25	3.74	-0.86	0.15	-1.58	-0.16
29	4.51	-0.16	0.86	-0.88	0.54
28	4.88	0.20	1.21	-0.52	0.90

antiradical. However, carotenoids are better free radical scavengers than ommochromes, in terms of this mechanism.

The hydrogen atom transfer mechanism is thermodynamically possible for all ommochromes being studied. 3-hydroxykynurenine and ommatin-D react with the four free radicals considered in this analysis. Considering the values for D_0 and the reactivity of each ommochrome with free radicals, the best antiradical is ommatin-D and the worst is kynurenic acid. Compared with carotenoids and taking into account the hydrogen atom transfer mechanism; carotenoids are better antiradicals than ommochromes. The worst antiradical is kynurenic acid.

Ommatin-D is the best antiradical and it is also the ommochrome with the largest value for λ_{\max} (the redder molecule). These results are important and may help to elucidate the function of these molecules in the animal kingdom.

Acknowledgment This study was funded by DGAPA-PAPIIT, Consejo Nacional de Ciencia y Tecnología (CONACyT), and resources provided by the Instituto de Investigaciones en Materiales (IIM). This work was carried out using a NES supercomputer, provided by Dirección General de Cómputo y Tecnologías de Información y Comunicación (DGTIC), Universidad Nacional Autónoma de México (UNAM). We would like to thank the DGTIC of UNAM for their excellent and free supercomputing services. Yanet Romero thanks CONACyT by scholarship number 202990.

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