Theor Chem Acc (2010) 127:485–492
DOI 10.1007/s00214-010-0737-3

REGULAR ARTICLE

Are pterins able to modulate oxidative stress?

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Received: 9 October 2009 / Accepted: 12 February 2010 / Published online: 4 March 2010

Abstract Pterins (also known as pteridines) are common animal colorants that constitute heterocyclic compounds and have the highest nitrogen content of any pigment analyzed from animals. It has been reported that pterins modulate oxidative stress as these molecules are able to scavenge free radicals. Previous reports suggest three possible mechanisms that are responsible for scavenging free radicals; these are electron transfer (ET) reaction, hydrogen atom transfer (HAT) and radical addition. In this paper, the facility to scavenge free radicals (antiradical power) of pterins is analyzed, using density functional theory calculations and considering two possible mechanisms: ET and HAT. For the electron transfer process, considering the electron donor facility of the free radical scavenger molecules, vertical ionization energy of pterins indicates that the antiradical power of those pterins is lower than the antiradical power of any carotenoids (except for tetrahydrobiopterin). In terms of the HAT mechanism, the bond dissociation energy involved in the removal of one hydrogen atom from pterins is higher than for carotenoids (except for sepiapterin and 7,8-dihydrobiopterin). It can be expected that the most reactive molecules are those that have the smallest dissociation energy since the dissociation of the hydrogen atom is the first step of the reaction. This could indicate that some pterins are depicted as poorer antiradicals than carotenoids in terms of the HAT mechanism. Further studies focusing on the third mechanism (radical addition) and the kinetics of the reactions are necessary in order to fully understand the antiradical power of these substances. For this reason, work continues in order to clarify these aspects.

Keywords pterins · Animal pigments · Antioxidants · Radical scavengers · Free radicals · Oxidative stress

1 Introduction

Pterins (also known as pteridines) refer to the common yellow, orange, or red UV absorbent and fluorescent colorants that are present in insects, fishes, amphibians, reptiles and the irises of certain birds [1–5]. These are heterocyclic compounds and have the highest nitrogen content of any animal pigment described [1, 2, 6]. The role of pterins as immune cell protectors is well known, and it has been reported that pterins are able to modulate oxidative stress (reviewed in Ref. 6). It is relevant to analyze the antioxidant (antiradical) power of pterins since they belong to a class of heterocyclic compounds, which are present in a wide range of living systems and participate in significant biological functions. As not all the antioxidant molecules seem to have the same reactivity, it is important to compare pterins with other well known antioxidants as carotenoids (CAR) in terms of their free radical scavenger power.

Electronic supplementary material The online version of this article (doi:10.1007/s00214-010-0737-3) contains supplementary material, which is available to authorized users.

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Three mechanisms are described in the literature [7–14] as constituting radical scavenging: the electron transfer (ET) reaction, the hydrogen atom transfer (HAT) and the radical addition. In a previous work, a discussion of the ET for CAR suggested that antiradicals may act by either donating or accepting electrons [10–13]. In order to evaluate the second mechanism (HAT), in a previous work, we reported quantum chemical calculations [14] for several CAR. Antiradical power was evaluated by assessing CAR-H bond dissociation energy (BDE) and correlating BDE with the antiradical power of these substances. It was reported before for CAR [11–13] that there is not a direct link between the energetic values and the experimental kinetic results, due to the fact that usually experimental results describe the relationship between structure and kinetics, and it is well known that kinetics and energetics do not necessarily reach the same conclusions. However, a similar approach considering the BDE was used previously to explain the radical scavenging mechanism of other molecules [15, 16], and authors concluded that computed BDE can be correlated with the antioxidant activities of the compounds.

In spite of the existence of previous studies analyzing the properties of pterins [6, 17–24], no density functional investigations exist, which analyze the facility of these molecules to scavenge free radicals. In order to understand the antiradical power of pterins, it is necessary to study the electron transfer process (ET) and the H-atom abstraction for each important H atom within the molecule. For ET, the reaction is governed by the ionization energy and the electron affinity of both: the radical scavenger and the free radical. A good electron donor will have low ionization energy and will be able to donate an electron to a good electron acceptor, with high electron affinity. Concerning the HAT mechanism, the driving force is arising from the difference in binding energy of the H atom, between the scavenger and the radical. The lower the BDE value, the easier the H abstraction and this could be related to the antiradical power of the molecule. BDE values provide important information referring to the reactive position that allows us to compare the reactivity of different radical scavenger. Therefore, it is possible to consider relative efficiencies of the scavengers within the assumption that they work under the same mechanism. Thus, the main goal is to compare the electron transfer power and the H-atom abstraction of two classes of chemical compounds that are considered radical scavengers (CAR and pterins). To do this, we used quantum chemical calculations in order to asses the vertical ionization energy (VIE) and vertical electron affinity (VEA) for eight pterins that were reported as animal pigments [1, 2] (presented in Table 1), and to determine the bond dissociation energy (BDE) involved in the removal of one hydrogen atom from the pterins. An assessment of the BDE relating to several hydrogen atoms in each pterin allowed us to identify the hydrogen atom that can be dissociated with the lowest energetic cost, thus defining its reactive position. In this work, the antiradical power of eight pterins is analyzed in terms of VEA, VIE and BDE. The adiabatic Gibbs free energies for the ET reaction of pterins with three freeradicals ($HO^{\bullet}$, $HOO^{\bullet}$ and $O_2^{\bullet -}$) are also included.

2 Computational details

Density functional theory [25] as implemented in Gaussian 03 [26] was used for all calculations. Becke's 1988 functional, which includes the Slater exchange, along with corrections involving the gradient of the density [27] and Perdew and Wang's 1991 (BPW91) gradient-corrected correlation functional [28, 29] were employed in the calculations of complete optimizations, without symmetry constraints. D5DV basis sets were also used [30]. Harmonic frequency analyses permitted us to verify optimized minima. Several rotamers and tautomers were used as initial geometries for the optimization. The most stable structure in each case was re-optimized with the same functional and the 6-311 +G(d) basis set [31–33]. Single point energy calculations at these optimized geometries were computed with the same functional and the 6-311 +G(d) basis set [31–33] to obtain verticals IE and EA.

The thermal corrections to Gibbs free energies of the BPW91/6-311 +G(d) fully optimized stationary points were used to obtain the adiabatic Gibbs free energy of each species involved in the charge transfer reaction. The stationary points were modeled in gas phase (vacuum). To include the solvent effects, full geometry optimization was done using polarisable continuum model, specifically the integral equation formalism (IEF-PCM) [34–37] at BPW91/6-311 +G(d) level of theory, with water (wt) and benzene (bz) as solvents for polar and non-polar environments, respectively.

Geometry optimization was applied to the radical scavengers, beginning with the optimized structure of the parent molecule after the H atom had been removed. The homolytic dissociation energy (BDE) of the H atom was calculated, as expressed in the following equation:

$$L - H \rightarrow L^{\bullet} + H^{\bullet}$$

$$BDE = [E((L^{\bullet}) + E(H^{\bullet})] - E(L - H) \quad (1)$$

where $L^{\bullet}$ denotes the L radical scavenger missing one H atom, and L − H is any molecule presented in Table 1. Our computational protocol was previously validated [14], comparing the theoretical values with available experimental values for vitamin E. Similar methodology was also

Table 1 Results for pterins. Vertical (VIE and VEA) and adiabatic (IEad and Ead) values (in eV) in water (WT) and benzene (BZ), for the eight pterins that we considered in this study

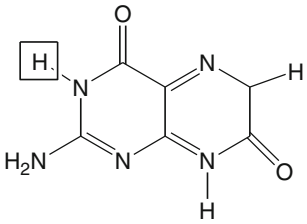
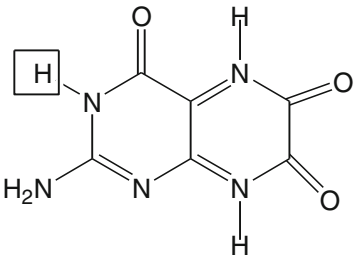
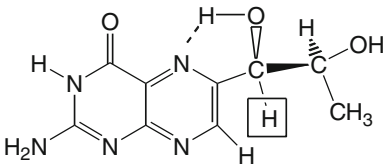
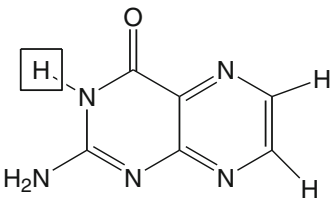
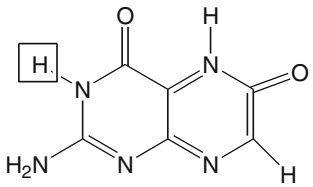
Molecular name	Molecular structure	WT		BZ	
		VIE *IEad*	VEA *EAed*	VIE *IEad*	VEA *EAad*
Isoxanthopterin (7-Xap)		6.3 *6.0*	2.7 *2.6*	7.1 *6.9*	1.7 *1.7*
Leucopterin (LCP)		5.8 *5.5*	2.5 *2.5*	6.8 *6.4*	1.6 *1.6*
Biopterin (BIP)		6.3 *5.9*	3.0 *2.9*	7.0 *7.0*	2.1 *2.1*
pterin (Ptr)		6.4 *6.2*	2.9 *2.8*	7.3 *7.0*	1.8 *1.9*
Xanthopterin (Xap)		5.9 *5.6*	3.1 *3.1*	6.9 *6.6*	2.2 *2.3*

Table 1 continued

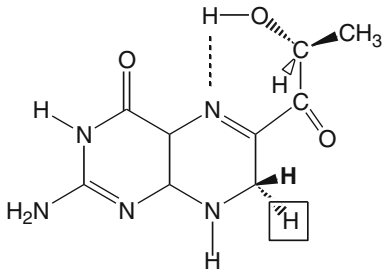
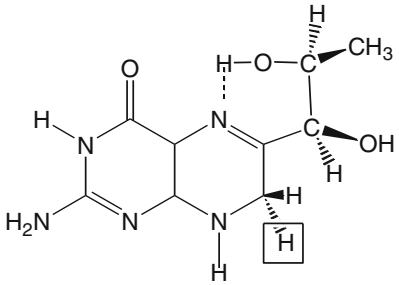
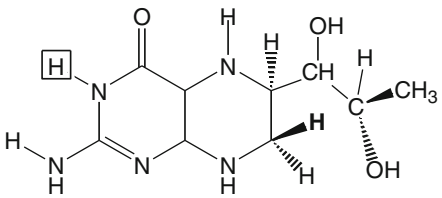
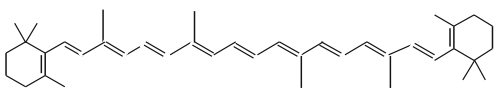
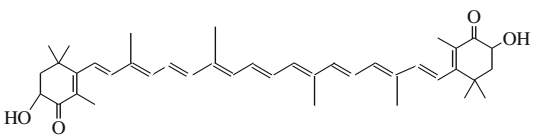
Molecular name	Molecular structure	WT		BZ	
		VIE *IEad*	VEA *EAed*	VIE *IEad*	VEA *EAad*
Sepiapterin (Sep)		5.8 *5.4*	3.0 *3.0*	6.6 *6.3*	2.1 *2.2*
7,8-dihydrobiopterin (H2Bip)		5.4 *5.1*	1.9 *1.5*	6.2 *5.9*	1.1 *1.3*
Tetrahydrobiopterin (BH4)		4.8 *4.2*	0.7 *1.2*	5.6 *5.0*	0.1 *0.4*
β-carotene* (BC)		4.6	2.7	5.1	2.1
Astaxanthin* (ASTA)		4.8	3.0	5.4	2.7
$HO^{\bullet}$			5.4 *5.2*		3.8 *3.7*
$HOO^{\bullet}$			4.2 *4.1*		2.7 *2.6*

Table 1 continued

Molecular name	Molecular structure	WT		BZ	
		VIE *IEad*	VEA *EAed*	VIE *IEad*	VEA *EAad*
$O_2^{\bullet -}$			3.8		2.3
			3.7		*2.3*

Electron affinity results are included for the free radicals that were considered. The molecular structure of each compound is schematically represented, also indicating the hydrogen atom that can be dissociated with the least energy cost (with a square). The IUPAC names are Isoxanthopterin (2-amino-1,8-dihydropteridine-4,7-dione); Leucopterin (2-amino-5,8-dihydro-1H-pteridine-4,6,7-trione); Biopterin (2-amino-6-(1,2-dihydroxypropyl)-7,8-dihydro-1H-pteridin-4-one); Pterin (2-amino-1H-pteridin-4-one); Xanthopterin (2-amino-1,5-dihydropteridine-4,6-dione); Sepiapterin (2-amino-6-[(2S)-2-hydroxypropanoyl]-7,8-dihydro-1H-pteridin-4-one); 7,8-dihydrobiopterin (2-amino-6-(1,2-dihydroxypropyl)-7,8-dihydro-1H-pteridin-4-one); and Tetrahydrobiopterin (2-amino-6-(1,2-dihydroxypropyl)-5,6,7,8-tetrahydropteridin-4(3*H*)-one). Vertical values previously reported [11–13] for BC and ASTA are included for comparison

* Reported previously on reference 10

used previously [17] to obtain the singlet excited states of pterins.

3 Results and discussion

Table 1 presents VEA and VIE for the eight pterins that we focused on in this study. The molecular structure for each compound is also schematically represented, indicating the hydrogen atom that is dissociated with the lowest energy cost. Adiabatic values (*IEad* and *EAad*) are also included. As can be seen, the difference between vertical and adiabatic values is very small and it is within the uncertainties inherent in the calculations. The expected error for this type of calculations is 0.2–0.4 eV. Since adiabatic values are similar to the vertical ones, and in order to be able to compare with previous results reported for carotenoids, the following discussion will consider only VIE and VEA. Figure 1 presents the results of VIE and VEA for pterins (in water and benzene) and for some CAR. BDE for pterins is presented in Fig. 2. In both figures, the results for CAR previously reported [11–14] are included for comparison.

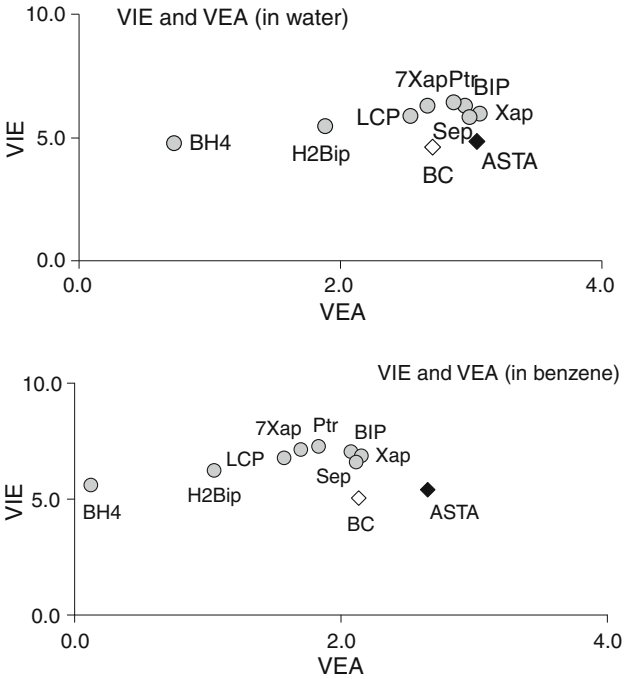


Fig. 1 Results for pterins (*gray circles*) included in Table 1. Results previously reported [11–13] for carotenoids (BC (*white diamond*) and ASTA (*black diamond*)) are included for comparison

3.1 Electron transfer mechanism (ET)

In order to trap, free radicals substances must either donate or accept electrons [11–13]. The propensity to donate or accept electrons can be analyzed using VIE and VEA. In terms of VIE, low values imply strong capability to donate electrons. For VEA, high values denote strong power to accept electrons. The results of VIE and VEA for pterins are reported in Table 1. Values for β-carotene (BC) and astaxanthin (ASTA) reported before are included for comparison. Taking VEA and VIE values, it is possible to position pterins and carotenoids (CAR) within a diagram that permits a straightforward qualitative comparison between substances. The diagram in water and benzene is shown in Fig. 1. As can be seen, the lowest value of VIE corresponds to BH4. Consequently, out of the molecules presented in Table 1, it is possible to conclude that BH4 is the best electron donor. Comparing the VIE results of pterins with those previously reported for CAR (see Ref.10), carotenoids have lower values. According to these results, CAR substances represent better antiradicals as electron donors than pterins. In order to complete the

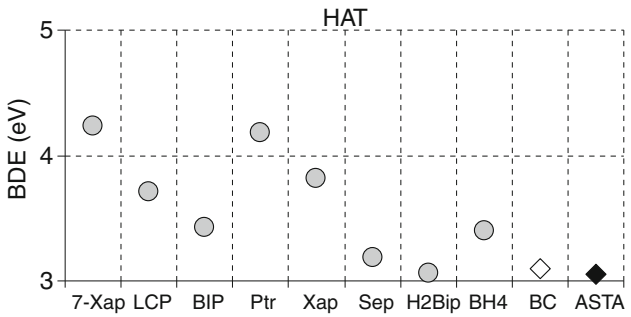


Fig. 2 BDE (H bond dissociation energy) of pterins. Values represent (*gray circles*) the dissociation energy (BDE in eV) for the H atom indicated in Table 1. The dissociation energy corresponds to the lowest value for each molecule (associated with the hydrogen atom indicated in Table 1). Results for some carotenoids (*β*-carotene (BC, *white diamond*) and astaxanthin (ASTA, *black diamond*)) reported before [14] are included for comparison

analysis, it is important to look at the antiradical capability in terms of the electron accepting power. In Table 1, it is possible to appreciate that the worst electron acceptor with the lowest VEA value is BH4. As a consequence, it can be concluded that BH4 is the worst radical scavenger when the electroaccepting power is taken into account. The VIE and VEA referring to the studied substances in water and benzene (Fig. 1) show that pterins in water are as good electron acceptors (similar values of VEA) as BC and ASTA (with the exception of H2Bip and BH4), but they are not as good electron donors as BC and ASTA (VIE values of pterins are higher than the correspondent values of CAR); in benzene, pterins are neither good electron donors nor good electron acceptors (only Sep, BIP and Xap have similar values of VEA than BC). Taking all these results and considering the electron transfer process, it can be expected that the antiradical power of those pterins reported in Table 1 (except BH4) could not be as good as the antiradical capability of CAR, which were studied [11–13] assuming that the free radical scavenger mechanism arises from electron donation to the free radical. If scavenging occurs from electron capture, the two classes of compounds may be equally good in water (except H2Bip and BH4), and Sep, Bip and Xap will be as good as BC in benzene.

To analyze in more detail the ET reactions, the energy evolution associated with the electron transfer process between pterins and free radicals was performed. The electron transfer mechanism that is expected for radical scavenger (*anti*) scavenging free radicals ($R^{\bullet}$) owing to the electron donor mechanism of the *anti* corresponds to

$$anti + R^{\bullet} \rightarrow anti^{\bullet+} + R^{-}\ Path\ I$$

Radical scavenger might also accept electrons according to the following reaction.

$$anti + R^{\bullet} \rightarrow anti^{\bullet-} + R^{+}\ Path\ II$$

Accordingly, the adiabatic Gibbs free energy at 298 K can be calculated with the subsequent equations:

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

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

We used three free radicals for this analysis: $HO^{\bullet}$ and $HOO^{\bullet}$ that could react according with *path I* [12] and $O_2^{\bullet-}$ that was reported as and example of *path II* with CAR [13]. These free radicals represent the most reactive molecules that could participate in the oxidative stress. The results are included in Table 2 (BC and ASTA previously reported are incorporated for comparison). As the values in Table 2 show, *path I* of pterins with $HO^{\bullet}$ and $HOO^{\bullet}$ is endergonic in water and benzene. It can be seen that it is exergonic with BH4, BC and ASTA in water and with $HO^{\bullet}$. This agrees with the conclusions that we can obtain from Fig. 1, since BH4, BC and ASTA are better electron donors than pterins. To analyze *path II*, it is necessary to see the reaction with $O_2^{\bullet-}$. Table 2 shows that it is exergonic for BC, ASTA and Xap in benzene, being more exergonic for ASTA than for the others. In water, all the reactions are endergonic. In benzene, Fig. 1 indicates that all pterins are worse electron acceptor but BIP, Sep and Xap have the same VEA value than BC. This correlates well with the adiabatic Gibbs free energies since the values are smaller for BIP, Sep, Xap and BC. The best electron acceptor (highest VEA value) is ASTA, and for this reason, the reaction of ASTA with $O_2^{\bullet-}$ is the most exergonic. The reaction of BIP with $O_2^{\bullet-}$ is endergonic, in agreement with available experimental data that indicates that BIP does not directly interact with superoxide free radical [6].

3.2 Hydrogen atom transfer mechanism (HAT)

In order to evaluate the hydrogen atom transfer (HAT) for pterins, BDE values are presented in Fig. 2. These results correspond to the dissociation energy of the hydrogen atom indicated in Table 1, which represents the lowest value for each molecule. To corroborate this statement, we calculated the dissociation energy of every hydrogen atom in each molecule (results are available as electronic supplementary material). Out of this group of pterins, Sep and H2Bip have the lowest BDE values and 7-Xap and Ptr the highest.

All pterins presented in Fig. 2 have higher BDE values than CAR, with the exception of Sep and H2Bip that have similar BDE values to BC and ASTA. This may indicate that Sep and H2Bip are as good radical scavengers as CAR, whereas other pterins represent the worst free radical scavengers (measured in terms of the HAT mechanism).

Table 2 Adiabatic Gibbs free energy (ΔG, kcal/mol) at 298.15 K for reactions I and II between pterins and free radicals ($HO^{\bullet}$, $HOO^{\bullet}$ and $O_2^{\bullet -}$). Results for BC and ASTA previously reported [11–13] are included for comparison

Molecular name	*Path I anti* + $R^{\bullet} \rightarrow anti^{\bullet +} + R^{-}$				*Path II anti* + $O_2^{-\bullet} \rightarrow anti^{\bullet -} + O_2$	
	$HO^{\bullet}$ (wt)	$HO^{\bullet}$ (bz)	$HOO^{\bullet}$ (wt)	$HOO^{\bullet}$ (bz)	Water	Benzene
Isoxanthopterin (7-Xap)	17.7	73.7	42.6	97.2	23.3	10.7
Leucopterin (LCP)	8.2	64.0	33.1	87.4	26.2	13.1
Biopterin (BIP)	18.2	77.5	43.1	100.9	19.5	3.2
pterin (Ptr)	22.4	75.8	47.4	99.3	18.9	8.0
Xanthopterin (Xap)	11.0	67.2	36.0	90.7	13.4	−0.7
Sepiapterin (Sep)	6.2	59.2	31.2	82.6	18.9	2.6
7,8-dihydrobiopterin (H2Bip)	0.5	52.5	25.4	75.9	51.3	20.9
Tetrahydrobiopterin (BH4)	−20.2	32.9	4.7	55.5	59.6	41.9
BC	−16.5	28.6	4.8	47.9	20.3	−0.2
ASTA	−12.5	36.0	8.8	55.3	11.5	−13.3

It is important to emphasize that in vivo the hydrogen atom dissociation reaction may be dominated by several aspects. The chemical environment and the solubility of the molecules are two aspects that may be important to define whether or not the reactive positions are available for the HAT reaction. The tendency of pterins to ring stack is something that must be considered in future works. Since free radical scavenger experimental parameters are not available, the only conclusion that we can obtain for the HAT mechanism is that the most reactive molecules could be those that have the smallest dissociation energy, because the dissociation of the H atom is the first step of the reaction for this mechanism. For this reason, it is possible to use BDE values in order to compare the reactivity of the molecules. Within this approximation, all the studied pterins could represent worse antiradicals than CAR in terms of the HAT mechanism, with two exceptions: Sep and H2Bip. Concerning the HAT mechanism, Sep and H2Bip represent the best free radical scavengers within the molecules reported in Table 1, and these two molecules manifest a similar free radical scavenger power to that of certain CAR. As it was previously reported for CAR [14], it appears to be a correlation between the number of reactive positions and the potential free radical scavenger power. All the pterins studied here have a single low-BDE hydrogen atom, i.e. just one reactive position, except Sep and H2BIP that have two H atoms with similar BDE values (see electronic supplementary material) This could increase the antiradical power of this pterin. It is clear that further experimental information is necessary in order to corroborate this hypothesis.

4 Conclusions

Figure 1 provides qualitative information concerning the electron transfer reactions. This is very useful, since it is possible to know the reaction path for the ET process. In a previous work, CAR were reported as good radical scavengers considering two ET reactions paths. It was described the electron affinity as very important since the viability of the reaction depends on the properties of both: the free radical and the radical scavenger. Regarding the ET process through the electron donor process, the antiradical power of those pterins (except BH4) is less than the antiradical power of some CAR. On the other hand, HAT mechanism and BDE values provide important information that permits us to characterize these systems. Within this mechanism, the only pterins that could be as good radical scavengers as CAR are Sep and H2Bip.

In order to understand the real value of pterins as protective antiradicals, it is crucial to fully comprehend the chemistry of these molecules. For this purpose, it is necessary to analyze the third reaction mechanism, namely radical addition to the pterins, in order to increase our understanding of the antiradical efficiency of these molecules. It is also necessary the analysis of the kinetic aspects of radical trapping. For this reason, work concerning these aspects is underway.

Acknowledgments This study was made possible due to funding from the Consejo Nacional de Ciencia y Tecnología (CONACyT), as well as resources provided by the Instituto de Investigaciones en Materiales IIM, UNAM. The work was carried out, using Kan-Balam supercomputer, provided by DGSCA, UNAM. We would like to thank The Dirección General de Servicios de Computo Académico (DGSCA) of the Universidad Nacional Autónoma de México for their excellent and free supercomputing services. We would also like to thank Caroline Karslake (Masters, Social Anthropology, Cambridge University, England) for reviewing the grammar and style of the text in English. The authors would like to acknowledge both Sara Jiménez Cortés and María Teresa Vázquez for their technical support. A.M. is grateful for financial support from the Ministerio de Educación y Ciencia de España (SAB2006-0192) and DGAPA-UNAM-México. A.B. was supported by the projects CGL2007-60369 and POL2006-05175 funded by the Spanish Ministry of Education and the European Regional Development Fund.

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