How Metal Influence on Reaction Mechanism of Antioxidants Considering the Solvent Effect: A DFT level Study

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Article

How Metal Influence on Reaction Mechanism of Antioxidants Considering the Solvent Effect: A DFT Level Study

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Abstract: Antioxidants are molecules that neutralize free radicals. In general, the reaction mechanisms of antioxidants are well known. The main reaction mechanisms of antioxidants are electron transfer (ET), proton transfer (PT), H atom transfer (HAT) and radical adduction (RAF). The study of these mechanisms is helpful to understand how antioxidants control high free radical levels on the cell. There are many studies focused on determine the main mechanism of an antioxidant to neutralize a wide spectrum of radicals, mainly reactive oxygen species (ROS) type radicals. Most of these antioxidants are polyphenols type compounds. Some esters, amides and metal-antioxidants have shown antioxidant activity. There are few experimental and theoretical studies about the antioxidant reaction mechanism of the aforementioned compounds. In this work, we shown the reaction mechanism proposed of an amide and its metal-antioxidant counterpart. We show how the presence of the metal increase the electron transfer on polar media and the H transfer in non-polar media. Even though, esters and amides are non-polar compound, the scavenger activity is good for the metal-antioxidant compound in no-polar media.

Keywords: reaction mechanism; solvent; antioxidant; metal influence

Introduction.

Within the development of new compounds for the treatment of diseases or conditions influenced by oxidative stress, synthetic antioxidants such as 2(3)-tert-butyl-4-hydroxyanizole (BHA), 2,5-di-tert-butyl-4-hydroxytoluene (BHT) [1,2], Edaravone [3] have been developed among others, which have been shown to have a good capacity as neutralizers of free radicals produced by oxidative stress. In addition to these compounds, a wide variety of compounds linked to metal groups have been developed, in which it has been shown that these compounds have greater biological activity as antioxidants [4,5]. For the synthesized series, *in vitro* tests of the antioxidant activity against different substrates (DPPH, $ABTS^{\cdot+}$, EDTA, FRAB) have been carried out, therefore with different methodologies, but not simulating the cellular environment. Therefore, the results have shown that the antioxidant activity varies according to the selected method. Studies on the mechanism by which radical neutralization is carried out for this type of compounds at an experimental and theoretical level are few [3].

To know the mechanism by which the neutralization of free radicals is carried out and its effectiveness, the theory of the transition state [6–9] and the Marcus theory [10] described by chemical kinetics are very useful. Within the reaction mechanisms that are studied in chemical kinetics are: the mechanism of electron transfer (ET), hydrogen transfer (HT) and the formation of adduct with the radical (FAR).

With the calculated values of the reaction energy ΔG^0 for each reaction channel (radical-molecule interaction site) and using the Marcus theory, the activation energy $\Delta G^{\ddagger}$ for the electronic transfer mechanism $\Delta G^{\ddagger}$ is obtained. With the value of k, the reaction rate constant is calculated using the transition state theory for the mechanism of electron transfer and hydrogen abstraction.

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Since the ˙OH, and ˙OOH radicals are transported in the cell medium by diffusion, the apparent rate constant k_{app} for the electron transfer mechanism was calculated.

The objective of this work is to evaluate the antiradical capacity from the modifications in the substituent linked to the metal center to determine the influence of the presence of the metal in the reaction mechanism and its efficiency as a radical scavenger of reactive oxygen species (ROS) simulating the cellular environment.

The presence of Sn(IV) in the p-coumaric acid molecule seems to contribute to increasing the reactivity in reaction channel 4a, with the ET mechanism being the one with the highest efficiency in polar media and HT in nonpolar media.

Computational details.

Khon-Sham approximation was used at Density Functional Theory [11,12] implemented in Gaussian 09 [13]. Truhlar M05 functional were employed [14]. 6-311+G (d, p) [15] basis set for N, O, C and H atoms and LANL2DZ pseudo-potentials and basis set [16–18] for Sn(IV) atom were also employed. The M05 functional has been recommended for kinetics calculation by its developers (14) for systems which commonly presents multireference character, and it has been successfully used by independent authors for that purpose [19–27]. Full geometry optimization for *p*-cumaric esters (Figure 1) were performed without symmetry constrains. Harmonic frequency analysis was made to verify optimized local minima and transitions states at the potential energy surface. Local minima have only real frequencies, while transition states have one negative frequency that corresponds to the expected motion along the reaction coordinate.

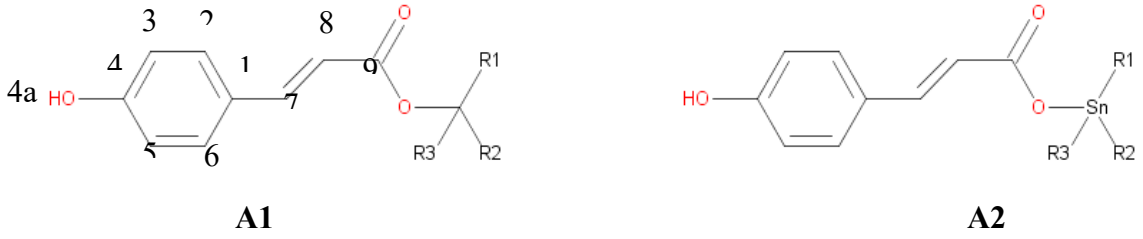

Figure 1. *ter*-butyl p-cumarate (A_1) and tri-butyl-tin *p*-cumarate (A_2).

Relative energies are computed with respect to the sum of the separated reactants. Solvent effect is taken into account to describe the molecular and biological system and their properties, due to its important role in biochemical process. Solvent effects are considered employing the SDM continuum model [28] using water and pentylethanoate as solvents, to mimic de cellular environment. The solvent cage effect has been considered according to the correction proposed by Okumo [29], taking into account the free energy volume theory [30]. Both corrections described above are in good agreement with those obtained by Ardura et al [31] and successfully used by other authors [32–38]. The expression used to correct Gibbs free energy is.

$$\Delta G_{sol}^{FV} \cong \Delta G_{sol}^{0} - RT\{ln[n10^{(2n-2)}] - (n-1)\} \quad (1)$$

where n is the molecularity of the reaction. According to equation 1, the cage effect in solution causes ΔG to decrease by 2.54 kcal/mol for bimolecular reactions, at 298.15 K.

The rate constant (k) was computed employing the conventional transition state theory (TST) [39–41] and 1 M standard state as

$$k = \sigma\tau\frac{k_B T}{h}e^{-(\Delta G^{\ddagger})/RT} \quad (2)$$

Where k_B and h are the Boltzmann and Plank constants, respectively, T is the temperature in K, R is the universal gas constant, $\Delta G^{\ddagger}$ is the activation energy, σ represents the reaction path degeneracy, accounting for the number of equivalent reaction path, and τ accounts for the tunneling correction, defined as the Boltzmann average of the ratio of the quantum and the classical probabilities, they were computed using the zero-curvature tunneling correction (ZCT) [42](38). TST

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has been proven to be enough for properly describing chemical reactions between free radicals and antioxidants [43].

For the mechanism involving single electron transfer (ET), the Marcus theory was employed [44,45] to calculate the energy barrier of activation $\Delta G^{\ddagger}$ in terms of two thermodynamic parameters, the free energy of reaction (ΔG^0) and the nuclear reorganization energy (λ)

$$\Delta G_{ET}^{\ddagger} = \frac{\lambda}{4}\left(1 + \frac{\Delta G_{ET}^{0}}{\lambda}\right)^2 \quad (3)$$

Where λ is calculated as:

$$\lambda = \Delta E_{ET} - \Delta G_{ET}^{0} \quad (4)$$

Where, ΔE_{ET} is the non-adiabatic energy difference between reactants and vertical products. Some of the calculated rate constants (k) values are close to diffusion-limit. Accordingly, the apparent rate constant cannot be directly obtained from TST calculations. In the present work the Collins-Kimball Theory [46] is used to correct the rate constant, and k_{app} is calculated as:

$$k_{app} = \frac{k_D k}{k_D + k} \quad (5)$$

Where k is the thermal rate constant computed by TST calculation, and k_D is the steady-state Smoluchowski rate constant for an irreversible bimolecular diffusion-controlled reaction:

$$k_D = 4\pi R D_{AB} N_A \quad (6)$$

Where R denotes the reaction distance, N_A is the Avogadro number and D_{AB} is the mutual diffusion coefficient of the reactants A (free radical) and B (*p*-cumaric ester). D_{AB} is computed from D_A y D_B according to reference [47], D_A y D_B have been estimated from the Stokes-Einstein approach [48].

$$D = \frac{k_B T}{6\pi\eta a} \quad (7)$$

Where t is the temperature, η the viscosity of the solvent, in our case water (η = 8.91 x 10^{-4} Pa s) and pentylethanoate (η = 8.62 x 10^{-4} Pa s); and a is the radius of the solute.

Direct reaction branching ratios (Γ) are computed as:

$$\Gamma_{path} = \frac{k_{path}}{k_{overall}} x100 \quad (8)$$

We have chosen the average reported pKa for *p*-cumaric acid (4.38) [49], to obtain the pKa for *ter*-butyl *p*-cumarate and tri-butyl-tin *p*-cumarate by using the method proposed by Ho [50]

$$pKa = \frac{\Delta G_{ani}^{0}}{RTLn(10)} + \left(pKa_{ref}\right) \quad (9)$$

Where ΔG_{ani}^{0}, is the anion free energy formation and pKa_{ref} is the pKa of the most similar acid. Thus, in aqueous solution at pH = 7.4, the neutral form of *ter*-butyl *p*-cumarate (A1) and tri-butyl-tin *p*-cumarate (A2) would predominate (97.7% and 97.6% respectively) over the deprotonated form (A_1^- 2.3 % and A_2^- 2.4 % respectively). In this work both, neutral and deprotonated, forms will be used to study their reactivity toward the considered free radicals in water, while in lipid media only the neutral form will be considered.

Results and discussion.

Reaction mechanism and kinetics for *ter*-butyl *p*-cumarate ester and its counterpart *tri*-butyl tin-*p*-cumarate ester, Figure 1, are shown. Once optimized ester geometries are obtained, multireference character is determined by a single point calculation employing CCSD method to compute the T1 parameter. T1 parameter is used to know multireference character of an organometallic complex [51,52] For neutral molecules, if the T1 value is higher than 0.023, they have mutireference and for

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transition state geometries, if T1 is higher than 0.044, they have multireference character. The T1 values for A1 and A2 was 0.032.

The theoretical calculations performed in this work address the following reaction pathways:

1.- Hydrogen transfer (**HT**)

A-H + R˙ → A˙ + R-H

2.- Radical adduct formation (RAF)

A-H + R˙ → [A-H-R]˙

3.- Single electron Transfer from neutral form (**SET-1**)

A-H + R˙ → A˙⁺ + R⁻

4.- Single electron transfer from deprotonated form (**SET-2**)

A⁻ + R˙ → A˙ + R⁻

In the **HT** mechanism we have considered the Hydrogen atom abstraction from the hydroxyl group at the position 4, and the abstraction of the hydrogen atoms bounded to carbons at the 7 and 8 positions. The object of the present work is to determinate how the presence of the Sn(IV) influences the different reaction mechanism and their rate constants in the reaction of **A1** and **A2** with the ˙OOH and ˙OH free radicals, in water and in lipid media. The thermochemical feasibility of the different mechanism and channels of reaction was investigated first, since it determinates the viability of chemical process.

For **A1** and **A2** molecules, pKa values, mol fraction in aqueous solution, bond dissociation energy (BDE) for hydrogen atoms on reaction channels 7 (C7), 8 (C8) and OH on C4 reaction channel for the HT**-1** mechanism, in water and pentylethanoate media, was computed and shown in Table 1.

Table 1. pKa, mol fraction in aqueous solution and Bond Dissociation Energy (BDE) in kcal/mol for **A1** and **A2** molecules.

Chanel	**37**(I)	**37**(II)	**38**(I)	**38**(II)
$\boldsymbol{pKa}$	9.011	-	9.014	-
Mol Frac.	0.023	-	0.024	-
BDE				
4a	70.53	76.61	70.90	70.59
7	89.85	90.92	91.49	90.80
8	100.33	98.70	164.65	99.64

(I)=water (II)= pentylethanoate.

BDE for channel 4a showed the lowest value in comparison with reaction channel 7 and 8, whereby channel 4a is energetically the most viable for **A1** and **A2**. BDE for the molecule **A2** slightly increases with the presence of the Sn(IV) moiety.

Single electron transfer (SET) mechanism.

Relative reaction Gibbs free energy values (ΔG^0) for the **SET-1** and **SET-2** mechanisms, calculated at 298.15 K in water and pentylethanoate with radical ˙OOH and ˙OH, are shown in Table 1.

Table 2. Reaction Gibbs free energy (ΔG^0), in kcal/mol, with the ˙OOH and ˙OH radical, in water and pentylethanoate at 298.15 K.

Channel	**A1**(I)		**A1**(II)		**A2**(I)		**A2**(II)	
	ΔG^0		ΔG^0		ΔG^0		ΔG^0	
	˙OOH	**˙OH**	**˙OOH**	**˙OH**	**˙OOH**	**˙OH**	**˙OOH**	**˙OH**
SET-1	26.04	0.62	64.88	41.35	26.54	0.82	68.21	44.67
SET-2	2.62	-22.97	-	-	0.81	-24.91	-	-

(I) =water (II) =pentylethanoate.

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For the **SET-1** mechanism, where the radical cation is formed from neutral geometry, the reaction Gibbs free energy (ΔG^0), in aqueous solution, with the radical ˙OOH is highly endergonic for **A1** and **A2** and the reaction is not viable. With ˙OH radical, the reaction is slightly endergonic. Activation energy $\Delta G^{\ddagger}$ values for **A2** reaction with ˙OH radicals decrease with respect to **A1**. The rate order of the apparent rate constant k_{app} for reaction of **A1** and **A2** with ˙OH radical doesn´t change, 10^9 M^{-1} s^{-1}, showing that the presence of the Sn(IV) in A2 contributes to decrease the height of the barrier but not to decrease the width, which is essential in the electron tunnel effect, but this contribution do not influence to improve the scavenger activity.

In pentylethanoate ΔG^0 is highly endergonic with both ˙OOH and ˙OH radicals because the formation of the ionic specie is not viable. Comparing ΔG^0 behavior of **A1** and **A2** in their neutral form, an increase in ΔG^0 is shown with the ˙OOH and ˙OH radicals in aqueous and lipid media. This shows that the presence of the Sn(IV) in the organometallic moiety acts like an electro-acceptor group, withdrawing electron density to the ester.

For the **SET-2** mechanism ΔG^0 is endergonic with the radical ˙OOH and highly exergonic with the radical ˙OH. For **A2**, which has a Sn(IV), ΔG^0 is less endergonic in the reaction with ˙OOH radical and more exergonic with ˙OH radical, in comparison to **A1**. It shown that the organometallic moiety acts like an electron-donor group, donating electron density to the ester in their deprotonated form favoring the charge transfer. Contrary to that shown for **SET-1** mechanism.

Activation energy $\Delta G^{\ddagger}$ values on the reaction of **A2** with ˙OOH radical, slightly decreases in comparison with **A1**. On the other hand, on the reaction of **A2** with ˙OH radical, $\Delta G^{\ddagger}$ decreases considerably in comparison with **A1**.

Table 3. Reaction Gibbs activation energy $\Delta G^{\ddagger}$ in kcal/mol, apparent rate constant k_{app} in M^{-1} s^{-1}.

	A1(I)		**A2**(I)	
SET-1	$\Delta G^{\ddagger}$	k_{app}	$\Delta G^{\ddagger}$	k_{app}
˙OOH	-	-	-	-
˙OH	1.28	8.55×10^{9}	0.34	8.78×10^{9}
SET-2	$\Delta G^{\ddagger}$	k_{app}	$\Delta G^{\ddagger}$	k_{app}
˙OOH	4.65	1.25×10^{6}	4.03	9.13×10^{7}
˙OH	44.41	8.53×10^{-24}	28.40	2.12×10^{8}

(I)= water.

With respect to the apparent rate constant k_{app} for reaction of **A1** and **A2** with ˙OOH and ˙OH radicals, the order of k_{app} increases from 10^6 M^{-1} s^{-1} to 10^7 M^{-1} s^{-1} on the reaction with radical ˙OOH and, from 10^{-24} M^{-1} s^{-1} to 10^8 M^{-1} s^{-1} for reaction with radical ˙OH. Therefore, the presence of Sn(IV) contributes to improve the reactivity of the ester increasing its efficiency like a scavenger. The order of k_{app} for **A2** with the radical ˙OOH, is comparable with that shown by glutation ($2.7\,10^7$ M^{-1} s^{-1}) [53] and the propensulphonic acid (2.6×10^7 $M^{-1}s^{-1}$) [54].

Hydrogen Transfer (HT) Mechanism.

Gibbs free energy values ΔG^0 in kcal/mol for **HT** mechanism, regarding reaction channels 4a, 7 y 8 in aqueous media are shown in Table 1. On reaction of **A1** y **A2** with radical ˙OOH, ΔG^0 for reaction channel 7 y 8 is endergonic, in both, aqueous and lipid media. In reaction channel 7, ΔG^0 increases in water and decreases in lipid media with the presence of Sn(IV), which shows that the presence of Sn(IV) favored the reaction in lipid media. For reaction channel 8, the presence Sn(IV) on **A2** contribute to increase ΔG^0, even in water and lipid media. Therefore, reaction channel 8 is the less favored.

Table 4. Reaction Gibbs free energy ΔG^0 in kcal/mol for A1 and A2 esters with radical ˙OOH and ˙OH.

	A1(I)	**A1**(II)	**A2**(I)	**A2**(II)

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4a				
˙OOH	-6.65	1.75	-6.27	-4.27
˙OH	-41.92	-33.94	-42.04	-39.97
7				
˙OOH	12.67	16.06	14.31	15.93
˙OH	-23.09	-19.64	-21.46	-19.76
8				
˙OOH	23.16	23.85	87.47	24.79
˙OH	-12.11	-11.86	51.71	-10.92

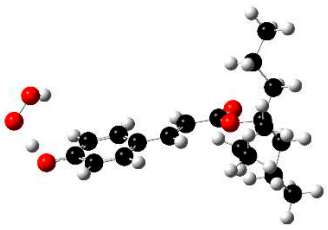
(I)=water (II)= pentylethanoate.

On the other hand, reaction with ˙OH radical, ΔG^0 in reaction channels 7 y 8 is exergonic, except for **A2** on water, where ΔG^0 is highly endergonic. In aqueous and lipid media, an increase in ΔG^0 for reaction channel 7 on **A2** is show in presence of Sn(VI) in comparison with **A1**. For reaction channel 8, ΔG^0 is exergonic on **A1** in water and lipid media. For **A2**, the presence of the Sn(IV) increases considerably ΔG^0 in water media. In lipid media the presence of Sn(IV) on **A2** contributes to increase ΔG^0, showing that channel 7 is more viable than channel 8, and that the presence of the Sn(IV) contributes to increase ΔG^0 of **HT** mechanism.

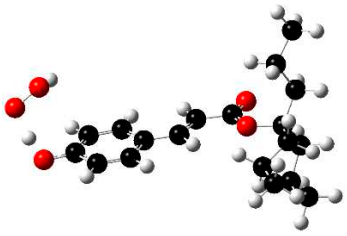
For reaction channel 4a, ΔG^0 is exergonic for the reaction with radical ˙OOH on **A1** (except in lipid media) and **A2**. On water, Gibbs free energy ΔG^0 slightly increases with the presence of Sn(IV). In pentylethanoate, ΔG^0 is endergonic for **A1,** and exergonic when Sn(IV) is present on **A2**, showing that the presence of Sn(IV) influences the transferring of light atoms like H.

For reaction with radical ˙OH, ΔG^0 is exergonic, even higher than that shown on channel 7 y 8, therefore, reaction channel 4a is the most viable, in both, pentylethanoate and water media. When Sn(IV) is included in **A2**, ΔG^0 is more exergonic than **A1**, which means, that the presence of the Sn(IV) contributes to increase the hydrogen transfer in both media.

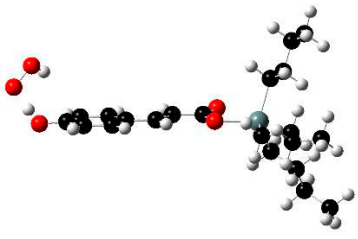
For hydrogen transfer mechanism, transition state geometries were optimized for **A1** and **A2** with ˙OOH radical, verifying that each transition state has a negative frequency corresponding to the reaction coordinate. Transition state geometries, for reaction with ˙OH radical, cannot be obtained. Even their ΔG^0 are highly exergonic, and it is probably that the reaction is carried out by diffusion.



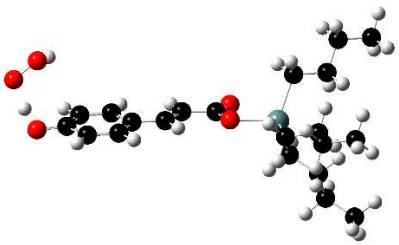
A1$_{(I)}$ F.I: = -3508.57



A1$_{(II)}$ F.I. = -3614.22



A2$_{(I)}$ F.I. = -3835.57



A2$_{(II)}$ F.I. = -1902.3134

Figure 2. Optimized transition state geometry of **A1** and **A2** with radical ˙OOH in water (I) and pentylethanoate (II) and their imaginary frequencies.

Activation energy $\Delta G^{\ddagger}$ and rate constant *k* were computed and show in Table 6. For reaction of **A1** and **A2** with ˙OOH radical on water, computed values of $\Delta G^{\ddagger}$ were 13.07 y 12.26 kcal/mol

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respectively. With respect to k, computed values were 1.24x10^6 y 4.64x10^6 M^{-1} s $^{-1}$, for **A1** and **A2** respectively. Even though, the presence of the Sn(IV) on **A2** contribute to decrease the $\Delta G^{\ddagger}$ barrier, the rate order of k remains without change. It can be due to the presence of the metal, which contribute to decrease the activation energy barrier, but do not contribute to modify the width of the barrier during the tunnel effect through the hydrogen transfer.

Table 5. Activation energy barrier $\Delta G^{\ddagger}$ in kcal/mol and rate constant k in M^{-1} s $^{-1}$.

	A1$_{(I)}$		**A1**$_{(II)}$		**A2**$_{(I)}$		**A2**$_{(II)}$	
	$\Delta G^{\ddagger}$	k	$\Delta G^{\ddagger}$	k	$\Delta G^{\ddagger}$	k	$\Delta G^{\ddagger}$	k
˙OOH	13.07	1.24x10^6	18.47	4.12x10^3	12.26	4.64x10^6	12.56	1.25x10^5

(I)= water, (II)= pentylethanoate.

In pentylethanoate, $\Delta G^{\ddagger}$ for reaction of **A1** and **A2** were 18.47 and 12.56 kcal/mol respectively, and computed k values were of 4.12x10^3 M^{-1} s $^{-1}$ for **A1** and 1.25x10^5 M^{-1} s $^{-1}$ for **A2**. In non-polar face, it was shown that the influence of the Sn(IV) contributes to decrease the activation barrier improving the tunnel effect, and increasing the rate order on **A2**, which means that the presence of the metal contribute to improve its efficiency like scavenger, on this type of systems.

Reaction Abduct Formation (RAF)

On Table 7 computed values of total rate constant k_T are shown. Contribution of each rate constant, for electron transfer and hydrogen transfer mechanism, were included with ˙OOH and ˙OH radicals.

Table 6. Total rate constant k_T in M^{-1} s $^{-1}$.

	A1$_{(I)}$	**A1**$_{(II)}$	**A2** $_{(I)}$	**A2** $_{(II)}$
	k_T	k_T	k_T	k_T
˙OOH	2.5x10^6	4.12x10^3	9.59x10^7	1.25x10^5
˙OH	8.55x10^9	-	8.99x10^9	-

(I)=water, (II) =pentylethanoate.

Contribution of each mechanism in the scavenger activity of **A1** and **A2** was computed by calculating the contribution ratio.

$$\Gamma = \frac{k_i}{k_T} x100 \qquad ec.5$$

Where Γ is the contribution ratio, k_i is the rate constant of the reaction mechanism and k_T is the total rate constant. Rate contribution is represented in percentage, Table 8.

For the reaction of **A1** with ˙OH radical, the main contribution comes from SET-1 mechanism, which contribute with a 100 %, because of the very low-rate order of *k*, shown in SET-2 mechanism. On the other hand, in the reaction with **A2**, the contribution is 97.6 %, the lower contribution is due to the deprotonated specie, which contributes with a 2.36 %. This means that both esters are good scavengers in their neutral form.

Table 7. Contribution (Γ) of each mechanism to the scavenger activity.

	A1$_{(I)}$	**A1**$_{(II)}$	**A2**$_{(I)}$	**A2**$_{(II)}$
	Γ	Γ	Γ	Γ
SET-1				
˙OOH	-	-	-	-
˙OH	100		97.6	
SET-2				
˙OOH	50	-	95.2	-

˙OH	0	-	2.36	-
HT				
˙OOH	49.6	100	4.84	100
˙OH	-	-	-	-

(I)=water, (II) =pentylethanoate.

For reaction of A1 with OOH radical, SET-2 and HT mechanism contributes to almost the same rate, 50.4 % and 49.6 % respectively. With respect to A2, the contribution changes due to the presence of Sn(IV), where the main contribution comes from SET-2 mechanism with a 95.2 % and a 4.84 % from HT mechanism, showing that the presence of Sn(IV) contributes to significantly increase the donor electron character of the ester to neutralize peroxy radicals, but not the transfer of light atoms like hydrogen. In lipid media, the main contribution comes from HT mechanism, due to the ester cannot form ionic species. This shows that metal could improve the scavenger capability of the ester derived from *p*-cumaric acid against peroxy type radicals.

Conclusions.

The present studio shows, how the presence of Sn(IV) in an ester derived from the *p*-cumaric acid can contribute increasing or decreasing its scavenger capability. Due to the great electronegativity of the OH radical, it reacts with the ester in their neutral form with and without the presence of the Sn(IV), as shown in mechanism SET-1. In presence of the metal, is observed that rate constant increases in SET-2 mechanism showing that Sn(IV) contributes to improve the scavenger capability of the anion (deprotonated specie), even the main contribution comes from SET-1 mechanism. Similar behavior can be seen on TH mechanism, where the presence of Sn(IV) does not contribute to improve the scavenger capability. All the above in water. On the other hand, in lipid media, the presence of the Sn(IV) has a great influence in the rate constant order, improving its scavenger capability. Therefore, the presence of Sn(IV) contributes to the ester mainly in lipid media than in polar media.

In the reaction with ˙OOH radical, which is a more selective radical, the presence of Sn(IV) contributes to significantly improve their scavenger capability. In could be due to the presence of the Sn(IV) in the deprotonated form, which could contribute to increase the angle formed between the plane of the aromatic ring and the lone pair of the oxygen [55,56], which have shown that increase the electron donor capability in the scavenger activity of an antioxidant. This studio contribute to the study of the development of new drugs focuses on the treatment of deceases where oxidative stress has great influence.

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