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Physicochemical Insights on the Free Radical Scavenging Activity of Sesamol: Importance of the Acid/Base Equilibrium

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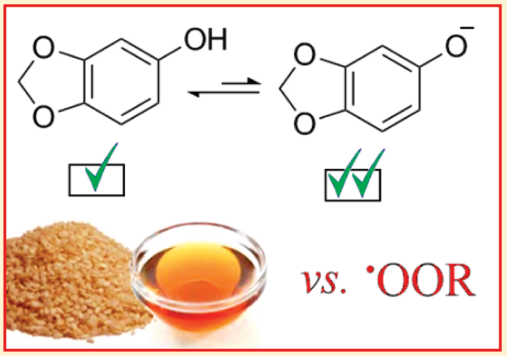
Supporting Information

ABSTRACT: Reactions of sesamol with different free radicals, in lipid and aqueous media, have been studied at the M05-2X/6-311+G(d,p) level of theory in conjunction with the SMD continuum model. Different mechanisms of reaction have been considered as well as polar and nonpolar environments. According to the overall rate coefficients, sesamol is predicted to react significantly faster in aqueous solution than in nonpolar media. The polarity of the environment also changes the relative importance of the reaction mechanisms. The anionic form of sesamol was found to be particularly reactive toward peroxyl radicals by transferring one electron. This mechanism was found responsible for the exceptional peroxyl radical scavenging activity of sesamol in aqueous solution, which was found to be even better than carotenoids, 2-propenesulfenic acid, and glutathione under physiological conditions. The agreement between experimental and calculated data supports the presented results as well as the methodology used in this work.



INTRODUCTION

Sesamol (1,3-benzodioxol-5-ol, SOH) is a natural antioxidant present in sesame seeds and oil. The beneficial effects of this compound are abundant. It has been proven that SOH makes sesame oil more resistant to oxidation than other vegetables oils.[1,2] It has been proposed that SOH inhibits DNA breaks caused by radiation,[3,4] some stages of neoplacia[5] and mutagnesis,[6,7] and lipid peroxidation.[8] SOH has also been proposed to have aniti-inflamatory,[9,10] hepatoprotective,[10,11] neuroprotective,[10] and antiaging effects.[12] A very important beneficial aspect of SOH is its antioxidant activity, which was first reported more than 60 years ago.[13] Since then several studies have been devoted to study this particular protective effect of SOH.

Nakagawa et al.[14] studied the protective action of SOH against ultraviolet (UV) radiation in organic solvents. They found two different radical products: the sesamolyl radical (SO$^{\bullet}$) and another one, assumed to be a dimer radical. However, the latter appeared only after longer times of radiation. Therefore, they proposed that the antioxidant activity of SOH might be attributed to formation of the sesamolyl radical. Bussandri et al.[15] studied the photodissociation of sesamol in aqueous solution and found the sesamolyl radical but also a cyclohezadienyl-like radical. They call attention on the necessity of further investigations on the antioxidant activity of SOH. More recently, Nakagawa identified at least another radical, a benzoquinone anion radical, after continuous UV radiation to sesamol in aqueous solution.[16] He also pointed out the importance of knowing in detail the intermediates to properly evaluate the antioxidant activity.

Kaur and Saini[6] proposed that the antioxidant activity of SOH is responsible for the strong antimutagenic effects of this compound. They demonstrated the hydroxyl and superoxide free radical scavenging of SOH using in vitro test systems. They also showed that SOH has no toxic effects at the tested doses. The hydroxyl and superoxide radical scavenging activity of SOH has also been proven by Kanimozhi and Prasad[17] using in vivo studies. Kim et al.[18] showed that SOH has strong antiphoto-oxidative activity, comparable to that of δ-tocopherol. They also proposed that SOH could be used to prevent photo-oxidation of oils, oil-soluble vitamins, and other oil-soluble compounds such as cholesterol, limonene, terpenes, etc. Very recently, Hayes et al.[19] proposed that the potency of SOH as antioxidant is higher than that of olive leaf extract and lutein.

Regarding the kinetics and mechanism of the free radical scavenging activity of SOH there is a very thorough experimental study by Joshi et al.[20] They demonstrated that SOH efficiently

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scavenges hydroxyl ($^{\bullet}OH$), trichloromethyl peroxyl ($^{\bullet}OOCCl_3$), lipid-peroxyl ($LOO^{\bullet}$), and tryptophanyl ($Trp^{\bullet}$) radicals in aqueous solutions. For the reaction with $^{\bullet}OH$ they estimated a rate constant of $1.1 \times 10^{10}\ M^{-1}\ s^{-1}$ at pH = 6.8. They also identified two UV bands corresponding to the formed products: one at 440 nm and another one at 350 nm, which were assigned to formation of $SO^{\bullet}$ and a radical adduct, $[SOH-OH]^{\bullet}$, respectively. They estimated that $SO^{\bullet}$ represents about 44% of the formed products. For the reaction with $^{\bullet}OOCCl_3$, also at pH = 6.8, the rate constant was found to be $3.7 \times 10^{8}\ M^{-1}\ s^{-1}$ and the UV at 440 nm was observed. In this case ~88% of the formed products was attributed to $SO^{\bullet}$. The SOH + $LOO^{\bullet}$ reaction was conducted at pH = 11, i.e., with the anionic form (SO^{-}) of sesamol, which has a $pK_a = 8.75$. Under such conditions the rate constant was estimated to be $3 \times 10^{8}\ M^{-1}\ s^{-1}$ and was attributed to the electron transfer from SO^{-} to the peroxyl radical. On the basis of its versatility as free radical scavenger, together with its nontoxicity, its solubility in both aqueous and lipid phases, and its stability at high temperatures, these authors proposed that SOH is a potent antioxidant under physiological conditions as well as in edible oils.

The information gathered so far strongly supports that sesamol can be very efficient as a free radical scavenger. Since the oxidative stress is a major health problem currently associated to the development of several diseases such as cancer,[21] cardiovascular disorders,[22] atherosclerosis,[23] and Alzheimer's disease,[24] the antioxidant activity of this compound deserves further studies. To the best of our knowledge, there are no previous theoretical studies dealing with the mechanisms and kinetics involved in the free radical activity of SOH. Therefore, it is the main goal of the present work to study the chemical reactions of this compound with the following radicals: $^{\bullet}OH$, $^{\bullet}OOH$, $^{\bullet}OOCCl_3$, and a model $LOO^{\bullet}$. To that purpose five mechanisms of reaction have been considered: single electron transfer (SET), sequential electron proton transfer (SEPT), sequential proton electron transfer (SPET), hydrogen transfer (HT), and radical adduct formation (RAF). The influence of the polarity of the environment on the reactivity of SOH toward the above-mentioned radicals has also been addressed, and branching ratios have also been estimated.

COMPUTATIONAL DETAILS

Geometry optimizations and frequency calculations have been carried out using the M05-2X functional[25] and the 6-311+G(d,p) basis set, in conjunction with the SMD continuum model,[26] using pentylethanoate and water as solvents to mimic lipidic and aqueous environments. The M05-2X functional has been recommended for kinetic calculations by their developers,[25] and it has been also successfully used by independent authors to that purpose.[27−34] Unrestricted calculations were used for open-shell systems, and local minima and transition states were identified by the number of imaginary frequencies (NIMAG = 0 or 1, respectively). In the case of the transition states it was verified that the imaginary frequency corresponds to the expected motion along the reaction coordinate by intrinsic reaction coordinate calculations (IRC). All electronic calculations were performed with the Gaussian 09 package of programs.[35] Thermodynamic corrections at 298 K were included in the calculation of relative energies.

The solvent cage effects have been included according to the corrections proposed by Okuno,[36] taking into account the free volume theory.[37] These corrections are in good agreement with those independently obtained by Ardura et al.[38] and have been successfully used by other authors.[39−45]

The rate constants (k) were calculated using conventional transition state theory (TST)[46] and 1 M standard state as

$$k = \sigma\kappa\frac{k_B T}{h} e^{-(\Delta G^{\ddagger})/RT} \quad (1)$$

where k_B and h are the Boltzmann and Planck constants, $\Delta G^{\ddagger}$ is the Gibbs free energy of activation, σ represents the reaction path degeneracy, accounting for the number of equivalent reaction paths, and κ accounts for tunneling corrections. The tunneling corrections, defined as the Boltzmann average of the ratio of the quantum and the classical probabilities, were calculated using the zero curvature tunneling corrections (ZCT).[47]

For the mechanisms involving electron transfer (ET) Marcus theory[48] was used. It relies on the transition state formalism and defines the ET activation barrier ($\Delta G^{\ddagger}_{ET}$) as

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

where ΔG^{0}_{ET} is the free energy of reaction and λ is a reorganization term.

Some of the calculated rate constants (k) are close to the diffusion limit. Accordingly, the apparent rate constant (k_{app}) cannot be directly obtained from TST calculations. In the present work the Collins−Kimball theory is used to that purpose[49]

$$k_{app} = \frac{k_D k_{act}}{k_D + k_{act}} \quad (3)$$

where k_{act} is the thermal rate constant, obtained from TST calculations (eq 1), and k_D is the steady-state Smoluchowski[50] rate constant for an irreversible bimolecular diffusion-controlled reaction

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

where R denotes the reaction distance, N_A is the Avogadro number, and D_{AB} is the mutual diffusion coefficient of reactants A (free radical) and B (antioxidant). D_{AB} has been calculated from D_A and D_B according to ref 51; D_A and D_B have been estimated from the Stokes−Einstein approach[52]

$$D = \frac{k_B T}{6\pi\eta a} \quad (5)$$

where k_B is the Boltzmann constant, T is the temperature, η denotes the viscosity of the solvent, in our case water ($\eta = 8.91 \times 10^{-4}$ Pa s) and pentylethanoate ($\eta = 8.62 \times 10^{-4}$ Pa s), and a is the radius of the solute.

The electronic spectra have been computed using the time-dependent density functional theory (TD-DFT) based on vertical excitations involving the three lowest lying excited states.

RESULTS AND DISCUSSION

The structure of SOH and the numbers assigned in this work to each site of reaction are shown in Figure 1. The antioxidant activity of this compound can take place through different mechanisms, as for many other compounds.[53−58] Those considered in this work are as follows.

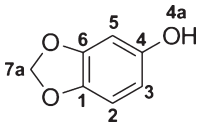

Figure 1. Sesamol (SOH) and numbered sites of reaction.

Single electron transfer (SET)

$$SOH + {}^{\bullet}R \rightarrow SOH^{\bullet+} + R^{-}$$

Hydrogen transfer (HT), from sites 4a and 7a

$$SOH + {}^{\bullet}R \rightarrow SOH(-H)^{\bullet} + HR$$

where SOH(−H) represents the radical formed when SOH loses a H atom.

Sequential electron proton transfer (SEPT)

$$SOH + {}^{\bullet}R \rightarrow SOH^{\bullet+} + R^{-} \rightarrow SO^{\bullet} + H^{+} + R^{-}$$

Radical adduct formation (RAF), on sites 1−6

$$SOH + {}^{\bullet}R \rightarrow [SOH-R]^{\bullet}$$

In addition it has been proposed that, at least for LOO radicals, the anionic form of sesamol (SO^{-}) is the reactive one and that its action takes place by electron transfer from SO^{-} to the peroxyl radical.[20] Accordingly, such process, which corresponds to a sequential proton electron transfer (SPET) mechanism, has also been considered in the present work. The energy evolution and the kinetic calculations involving this mechanism have been studied assuming that the rate-limiting step is the SET step, and the fractions of the neutral and anionic forms have been taken into account, as explained below. It is important to notice that this mechanism also yields the sesamolyl radical

Sequential proton electron transfer (SPET)

$$SOH \rightarrow SO^{-} + H^{+} \xrightarrow{+R^{\bullet}} SO^{\bullet} + R^{-} + H^{+}$$

Therefore, mechanisms HT (from site 4a), SEPT, and SPET all contribute to formation of $SO^{\bullet}$.

The Gibbs free energies of reaction (ΔG), at 298.15 K, for the different mechanisms and reaction sites involving SOH are provided in Table 1. As these values show, the SET mechanism is exergonic only for the reaction involving $^{\bullet}OH$ in aqueous solution, and it was found to be approximately isoergonic for the reaction of sesamol with $^{\bullet}OOCCl_3$. In addition, it should be noted that once the SOH radical cation is formed, the deprotonation process is predicted to occur spontaneously in aqueous solution from site 4a ($\Delta G = -5.19$ kcal/mol). Therefore, the observed product, formed via SET, would be the sesamolyl radical ($SO^{\bullet}$). This process actually corresponds to the sequential proton electron transfer (SEPT) mechanism. The deprotonation process involves the proton, and it is known that computational methods poorly reproduce the solvation energies of this particular species. Therefore, its Gibbs free energy in solution (ΔG_S) has been derived from experiments using

$$\Delta G_S(H^+) = \Delta G_g(H^+) + \Delta G_{Solv}(H^+) \quad (6)$$

where ΔG_g is the Gibbs free energy in the gas phase and ΔG_{Solv} is the Gibbs free energy of solvation. In this work we used

Table 1. Gibbs Free Energies of Reaction (ΔG), at 298.15 K, in kcal/mol

	pentyl ethanoate			water		
	$^{\bullet}OH$	$^{\bullet}OOH$	$^{\bullet}OOCCl_3$	$^{\bullet}OH$	$^{\bullet}OOH$	$^{\bullet}OOCCl_3$
SET				−2.48	20.60	0.24
HT						
site 4a	−38.49	−5.29	−11.71	−40.17	−7.41	−14.73
site 7a	−24.44	8.76	2.33	−25.52	7.25	−0.07
RAF						
site 1	−21.28	7.57	1.87	−21.53	6.45	−0.71
site 2	−11.38	16.41	9.63	−12.34	14.86	7.36
site 3	−15.44	11.59	5.53	−15.74	10.98	3.04
site 4	−18.84	9.50	3.44	−20.06	8.42	1.27
site 5	−12.80	15.81	11.11	−13.14	15.30	8.23
site 6	−20.38	8.37	2.13	−20.67	7.34	0.13

$\Delta G_g(H^+) = -4.39$ kcal/mol and $\Delta G_{solv}(H^+) = -265.89$ kcal/mol, based on the recommendation of Camaioni and Schwerdtfeger.[59]

It seems worthwhile to call attention on the fact that acid−base equilibria are assumed to be thermodynamically controlled, with the relative population of the acid and of the conjugated base governed by the pH of the environment and the pK_a of the acid. Since a ΔG value equal to −5.19 represents a negative pK_a, the preponderant form of the radical cation would be the deprotonated one at any pH of interest. Moreover, since there are no previous reports on the pK_a of $SOH^{\bullet+}$ we estimated its value using the proton exchange method, also known as the isodesmic method or the relative method,[60] which has been reported to produce reliable values of pK_a.[60−62] It involves the reaction scheme

$$HA + Ref^{-} \leftrightarrow A^{-} + HRef$$

where HRef/ref^{-} is the acid/base pair of a reference compound. This reference system should be as similar as possible to the one that is being investigated. Within this approach the pK_a is calculated as

$$pK_a(HA) = \frac{\Delta G_s}{2.303RT} + pK_a(HRef) \quad (7)$$

where the experimental value of the reference acid, HRef, is used. In this work we used the radical cation of melatonin ($MLT^{\bullet+}$) as HRef and its pK_a value equal to 4.7.[63] This reference system has been chosen since it represents an acid−base equilibrium similar in nature to the one we are studying, i.e., deprotonation of a radical cation. Accordingly, our reaction scheme is

$$SOH^{\bullet+} + MLT^{\bullet} \leftrightarrow SO^{\bullet} + MLT^{\bullet+}$$

The experimental data on the acid constants of this kind of species (radical cations) are extremely scarce due to their very short lifetime. Therefore, we could not find a better reference system. At the same time this lack of information increases the importance of reporting estimations of the pK_a values for such species. According to our results the pK_a of $SOH^{\bullet+}$ was found to be equal to −1.3. This demonstrated that under physiological conditions and at most pH in the usual ranges its dominant form would be the deprotonated one, i.e., the SO radical. Moreover, the population of the radical cation would be so low that it would

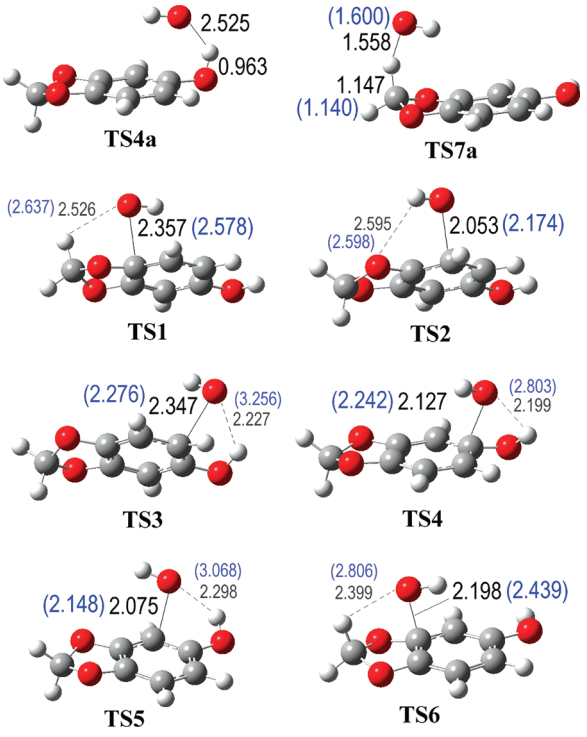

Figure 2. Optimized geometries of transition states involved in the SOH reaction with $^{\bullet}$OH, in penthyletanoate (water) solution. HT: TS4a, TS7a. RAF: TS1, TS2, TS3, TS4, TS5, and TS6. Distances are reported in Angstroms.

be negligible at physiological pHs and thus very difficult to be experimentally observed.

For the SOH + $^{\bullet}$OH reaction, the HT and RAF mechanisms were found to be exergonic, regardless of the reaction site and of the polarity of the environment. This is in line with the known high reactivity of this radical. The largest exergonicity corresponds to the HT channel 4a, which is the one yielding SO$^{\bullet}$. In addition the HT channels are more exergonic than the RAF channels, both in lipid and in aqueous media. For the SOH reaction with $^{\bullet}$OOH, the least reactive of the studied radicals, there is only one channel of reaction thermochemically viable (channel 4a). Therefore, for this particular reaction only one product is expected to be observed, the sesamolyl radical, regardless of the polarity of the environment. For the SOH + $^{\bullet}OOCCl_3$ reaction, there is also only one exergonic channel (4a) in lipid media, but in aqueous solution HT from site 7a and RAF on site 1 were found to have slightly negative values of ΔG and can be considered at least isoergonic. In general, the thermochemical viability of the studied reactions increases in aqueous solution, suggesting that a polar environment favors the reactivity of sesamol toward free radicals.

For the reactions of SO^{-} with $^{\bullet}$OH, $^{\bullet}$OOH, $^{\bullet}OOCCl_3$, and LOO$^{\bullet}$ the Gibbs free energies of reaction, in aqueous solution, were found to be −26.00, −2.91, −23.27, and 0.24 kcal/mol, respectively. The reactions involving the anionic form of sesamol have only been considered in aqueous solution, since in nonpolar media the deprotonation process is negligible. The $CH_3-CH(OO^{\bullet})-CH=CH-CH_3$ radical has been used to model the lipid peroxyl radical. According to our results peroxyl radicals (ROO$^{\bullet}$) seem to be able to react via SET with the sesamol anion in aqueous solution. For other antioxidants the SET process only becomes viable when R is a group with high electron-withdrawing character. However, in this case it is also proposed to be possible when R = H, alkyl, or alkenyl groups and more important for lipid peroxyl radicals.

The channels of reaction described above as endergonic will no longer be considered in this work since, because even if they take place at a significant rate, they would be reversible and therefore the formed products will not be observed. However, it should be noticed that they might still represent significant channels if their products rapidly react further. This would be particularly important if these later stages are sufficiently exergonic to provide a driving force and if their barriers of reactions are low. In addition, it should be noticed that even when endergonic processes might play important roles in biological systems, this particular behavior appears only when there are not parallel reactions more energetically favored.

The fully optimized geometries of the transition states (TS) corresponding to the SOH + $^{\bullet}$OH reaction are shown in Figure 2. In general, the TSs are earlier in aqueous solution, suggesting a reactivity increment with the polarity of the environment. Some of the TSs corresponding to the RAF mechanism present weak H-bond-like interactions, which are weaker in water solution compared to lipid media. Moreover, the interaction distance becomes larger than 3 Å for TS3 and TS5. This means that the interaction actually vanishes in these cases. The corresponding distances are shown in Figure 2 for comparison purposes only. Regarding TS4a it was located and characterized in pentyl ethanoate solution; however, in aqueous solution it was not possible to locate a fully optimized TS. Using a partial optimization with frozen O−H and H−OH bond distances we were able to obtain a structure that presents a single imaginary frequency. Unfreezing these two distances, in a saddle-point optimization, invariably lead to an increase of the H−OH distance and the corresponding decrease of the imaginary frequency and gradient, yielding the separated reactants. A relaxed scan, obtained by decreasing the H−OH distance, produces a similar result: in this case, the energy decreases until the H atom is completely transferred. This means that the reaction is barrierless and strictly diffusion controlled, i.e., every encounter results in conversion of reactants into products.

For the TSs corresponding to the thermochemical viable channels of the SOH reaction with $^{\bullet}$OOH and $^{\bullet}OOCCl_3$ (Figure 3) no H-bond interactions were found. As described for the TSs involving $^{\bullet}$OH, the transition states were found to be earlier in water solution than in pentyl ethanoate solution. This indicates that the reactivity of SOH toward free radicals increases with the polarity of the environment regardless of the nature of the reacting radical.

The Gibbs free energies of activation ($\Delta G^{\ddagger}$) at 298.15 K are reported in Table 2 for reactions involving the neutral form of sesamol. As the data in this table show, for the SOH + $^{\bullet}$OH reaction RAF channels on sites 1 and 3 in nonpolar media and on sites 1, 3, 4, and 6 in water solution have $\Delta G^{\ddagger}$ values very close to zero. Moreover, taking into account the uncertainty inherent to every method of calculation, they can actually be considered barrierless. These are the channels with the lowest barrier for reactions of SOH with $^{\bullet}$OH. For the SOH + $^{\bullet}OOCCl_3$ reaction, in aqueous solution, the lowest barrier corresponds to RAF on site 1 followed by that of the SET process. In general, for every specific channel of reaction the lowest barrier corresponds to the reaction with $^{\bullet}$OH and the highest to the reaction with $^{\bullet}$OOH,

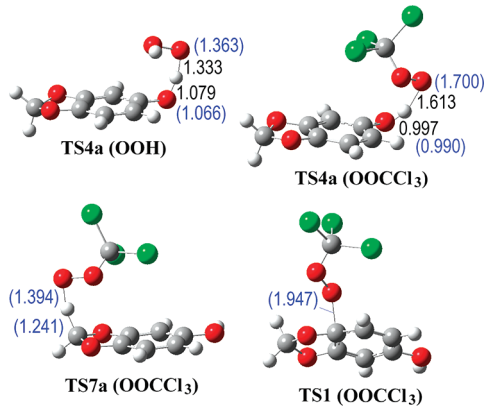

Figure 3. Optimized geometries of transition states involved in the SOH reaction with $^{\bullet}$OOH and $^{\bullet}$OOCCl$_3$, in penthyletanoate (water) solution. HT: TS4a, TS7a. RAF: TS1. Distances are reported in Angstroms.

with those involving $^{\bullet}$OOCCl$_3$ in between. This order is in line with the relative reactivity of these radicals.

For the SET reactions of the anionic form of sesamol with $^{\bullet}$OH, $^{\bullet}$OOH, $^{\bullet}$OOCCl$_3$, and LOO$^{\bullet}$ the Gibbs free energies of activation, in aqueous solution, were found to be 14.10, 3.27, 0.19, and 4.87 kcal/mol, respectively. For the reaction with $^{\bullet}$OH the barrier is significantly high since it corresponds to the inverted region of Markus theory ($\Delta G < -\lambda$).[64] In the particular case of the SO$^-$ + $^{\bullet}$OH reaction, ΔG is lower than $-\lambda$ by 19.4 kcal/mol. The electron transfer from SO$^-$ to $^{\bullet}$OOCCl$_3$ is also in the inverted region. However, in this case ΔG is lower than $-\lambda$ only by 3.8 kcal/mol. Therefore, it is very close to the vertex of the parabola and the barrier remains low (Figure 1S, Supporting Information).

The rate constants for the different channels of reaction are reported in Table 3, together with the overall rate coefficients ($k_{overall}$), which have been calculated as

$$k_{overall} = p^N k^N_{tot} + p^A k^A_{tot} \quad (8)$$

where p^N and p^A account for the fractions of the neutral and the anionic forms of sesamol, respectively, and were obtained from the reported pK_a value (8.75). The value of these fractions change with pH. At pH = 6.8, used in the experiments with $^{\bullet}$OH and $^{\bullet}$OOCCl$_3$, $p^N = 0.99$ and $p^A = 0.01$. At p H = 11, used in the experiments with $^{\bullet}$OOL, $p^N = 0.01$ and $p^A = 0.99$. At physiological pH (7.4), $p^N = 0.96$ and $p^A = 0.04$.

The total contributions of each form (k^N_{tot} and k^A_{tot}) have been estimated by summing up the rate constants of the different reaction channels of the viable mechanisms. For example, for reaction of sesamol with $^{\bullet}$OH in aqueous solution

$$k^N_{tot} = k^{N,SET}_{app} + k^{N,HT}_{app} + k^{N,RAF}_{app} \quad (9)$$

$$k^A_{tot} = k^{A,SET}_{app} \quad (10)$$

where

$$k^{N,HT}_{app} = k^{N,4a}_{app} + k^{N,7a}_{app} \quad (11)$$

$$k^{N,RAF}_{app} = k^{N,1}_{app} + k^{N,2}_{app} + k^{N,3}_{app} + k^{N,4}_{app} + k^{N,5}_{app} + k^{N,6}_{app} \quad (12)$$

Table 2. Gibbs Free Energies of Activation ($\Delta G^{\ddagger}$), at 298.15 K, in kcal/mol

	pentyl ethanoate			water		
	$^{\bullet}$OH	$^{\bullet}$OOH	$^{\bullet}$OOCCl$_3$	$^{\bullet}$OH	$^{\bullet}$OOH	$^{\bullet}$OOCCl$_3$
SET				1.25		5.65
HT						
site 4a	1.61	12.70	8.78	~0.0	13.52	7.60
site 7a	3.40			3.31		8.55
RAF						
site 1	0.30			0.60		3.61
site 2	6.11			1.99		
site 3	0.04			0.60		
site 4	2.88			0.80		
site 5	4.38			2.18		
site 6	2.23			0.62		

It should be noted that, as explained above, the SET products spontaneously transform into the SEPT products. However, since the first and slower step of this mechanism is the SET part, this step is the one used for calculation of the rate constant.

It should also be noted that the adduct formed through addition of $^{\bullet}$OOCCl$_3$ to site 1 is only 0.71 kcal/mol more stable than the reactants (Table 1). Therefore, the reverse reaction cannot be neglected and there is not an equation to calculate the corresponding rate coefficient. Moreover, since the reverse reaction is a unimolecular process the rate constants of the direct and the reverse reaction are not directly comparable. Thus, the behavior of such system would strongly depend on the reaction conditions, particularly on the concentrations of the reacting species. Under experimental and physiological conditions such concentrations are far below the standard state 1M, which means that the reverse process is favored. Consequently, pseudo-first-order equilibrium constants should be used to get an idea of the actual behavior under such conditions. Using this methodology we were able to explain similar cases in atmospheric chemistry.[65] For addition of $^{\bullet}$OOCCl$_3$ to site 1 in sesamol the latter is in excess; therefore, its concentration is the one remaining almost unchangeable in the pseudo-first-order model. Using the same sesamol concentration used in the experiments (5×10^{-4} M) we obtain a pseudo-firstorder equilibrium constant which is very small and equals 3.3×10^{-3}. According to this estimation only 0.3% is expected to remain as the addition product at equilibrium and that is considering this channel of reaction alone. Since under physiological conditions the concentrations of sesamol should be orders of magnitude lower than 5×10^{-4} M, adduct formation would be even less favored. Even if our equilibrium constant is underestimated, the error would cancel by the lower concentrations under physiological conditions. Therefore, we can safely conclude that the contribution of RAF at site 1 for the reaction with $^{\bullet}$OOCCl$_3$ is negligible under physiological conditions. It should be noticed however that under experimental conditions using higher concentrations of sesamol or in experiments directly involving sesame oil the outcome might be different.

According to the overall rate coefficients, SOH is predicted to react faster in aqueous solution than in nonpolar media. This increased reactivity is particularly important for the peroxyl radicals and arises from the capacity of the anionic form of sesamol to easily donate one electron. The overall rate

Table 3. Apparent Rate Constants of the Different Channels and Overall Rate Coefficient (M^{-1} s^{-1}) at 298.15 K[a]

	pentyl ethanoate			water			
	$^{\bullet}OH$	$^{\bullet}OOH$	$^{\bullet}OOCCl_3$	$^{\bullet}OH$	$^{\bullet}OOH$	$^{\bullet}OOCCl_3$	$^{\bullet}OOL$
SPET				2.87×10^2	5.71×10^9	7.40×10^9	1.36×10^9
SEPT				7.71×10^9		4.20×10^8	
HT							
site 4a	2.11×10^9	3.33×10^4	6.90×10^6	2.04×10^9	2.09×10^5	2.03×10^7	
site 7a	2.00×10^9			1.96×10^9		1.87×10^7	
RAF							
site 1	2.11×10^9			2.04×10^9		5.31×10^6	
site 2	3.45×10^8			2.03×10^9			
site 3	2.11×10^9			2.04×10^9			
site 4	2.07×10^9			2.04×10^9			
site 5	1.65×10^9			2.03×10^9			
site 6	2.10×10^9			2.04×10^9			
overall	1.45×10^10	3.33×10^4	6.90×10^6				
overall, p H = 7.4				2.29×10^{10}	2.44×10^8	7.60×10^8	3.89×10^7
overall, p H = 6.8				2.37×10^{10}	6.36×10^7	5.41×10^8	
exp.,[20] p H = 6.8				1.1×10^{10}		3.7×10^8	
overall, p H = 11							1.36×10^9
exp.,[20] p H = 11							3.0×10^8

[a] The overall rate coefficients include the fractions of the neutral and the anionic forms at the corresponding pHs.

coefficients in aqueous solution, at physiological pH, were found to be about 1.6, 7340, and 110 times higher than in nonpolar media for the reactions with $^{\bullet}OH$, $^{\bullet}OOH$, and $^{\bullet}OCCl_3$, respectively (Table 3).

The overall reactivity of SOH toward OH radicals was found to be diffusion controlled in lipid and aqueous solutions (1.45×10^{10} and 2.29×10^{10} M^{-1} s^{-1}, respectively), supporting the excellent $^{\bullet}OH$ scavenging activity of this compound, which is in agreement with the available experimental evidence. The efficiency of sesamol to scavenge $^{\bullet}OOCCl_3$ and $^{\bullet}OOH$ is predicted to be lower than that for scavenging $^{\bullet}OH$ but still exceptionally good. The order of reactivity with the studied radicals was found to be $^{\bullet}OH$ > $^{\bullet}OOCCl_3$ > $^{\bullet}OOH$, in line with their relative reactivity. The overall rate constants in aqueous solution with $^{\bullet}OOCCl_3$ and $^{\bullet}OOH$, at physiological pH, were found to be 7.60×10^8 and 2.44×10^8 M^{-1} s^{-1}, respectively. As the pH decreases, so does the fraction of the anionic form of sesamol; consequently, the overall rate constant becomes smaller.

The values of the overall rate coefficients reported in Table 3 indicate that sesamol is exceptionally good as a peroxyl radical scavenger, particularly in aqueous solution. In nonpolar environments the peroxyl radical scavenging activity of sesamol was found to be slightly lower than that of carotenes ($\sim 10^5$–10^6 M^{-1} s^{-1})[66] and canolol (6.8×10^5 M^{-1} s^{-1}),[67] similar to that of sinapinic acid (1.7×10^4 M^{-1} s^{-1})[68] and much higher than that of melatonin (3.1×10^2 M^{-1} s^{-1}),[69] and caffeine (3.2×10^1 M^{-1} s^{-1}).[58] In aqueous solution, the rate coefficient for the reaction of sesamol with $^{\bullet}OOH$ is much higher than carotenes ($\sim 10^5$–10^6 M^{-1} s^{-1}),[66] allicin ($\sim 8 \times 10^3$ M^{-1} s^{-1}),[70] and melatonin ($\sim 2 \times 10^1$ M^{-1} s^{-1})[69] and about 10 times higher than that of 2-propenesulfenic acid ($\sim 2.6 \times 10^7$ M^{-1} s^{-1})[70] and glutathione ($\sim 2.7 \times 10^7$ M^{-1} s^{-1}),[71] which are very good for scavenging $^{\bullet}OOH$. This radical has been chosen for this comparison due to its low reactivity, compared to other ROS. Moreover, precisely because of this low reactivity, overall rate coefficients on the order of 10^5 M^{-1} s^{-1} indicate that a chemical compound is a good radical scavenger and rate coefficients on the order of 10^8 M^{-1} s^{-1} imply an outstanding antioxidant activity.[72] It should be noticed than in addition to the relatively high rate constants, sesamol also presents other characteristics desirable for good antioxidants.[73] It can be present in both lipid and aqueous media, its size favored the transport across the membranes, it is nontoxic, and it is versatile in the sense that it is able to scavenge a wide variety of free radicals.

Despite the complexity of the studied systems, agreement with available kinetic experimental data is very good. The calculated rate coefficients were found to be only 2.15, 1.46, and 4.54 times larger than the experimental values[20] for the reactions SOH + $^{\bullet}OH$ (at pH = 6.8), SOH + $^{\bullet}OOCCl_3$ (at pH = 6.8), and SO^- + $^{\bullet}OOL$ (at pH = 11), respectively. This agreement supports the validity of the calculated data.

The branching ratios of the different channels of reaction are reported in Table 4. They represent the percent contribution of the different channels to the overall reaction and have been calculated as

$$\Gamma_i = \frac{k_i}{k_{\text{overall}}} \times 100 \qquad (13)$$

The reported values for aqueous solution correspond to physiological pH. As discussed before, in nonpolar media reactions of sesamol with $^{\bullet}OOH$ and $^{\bullet}OOCCl_3$ yield only one product, the sesamolyl radical (SO$^{\bullet}$), which is formed through HT from site 4a. Therefore, in these cases this channel represents 100% of the overall reaction. On the contrary, reaction with $^{\bullet}OH$, in the same kind of media is predicted to produce a wide variety of products, formed through HT and RAF mechanisms. Moreover, with the exception of the adduct formed at site 2, which is predicted to be

Table 4. Branching Ratios (Γ) of the Different Channels of Reaction at 298.15 K

	pentyl ethanoate			water[a]		
	$^{\bullet}$OH	$^{\bullet}$OOH	$^{\bullet}OOCCl_3$	$^{\bullet}$OH	$^{\bullet}$OOH	$^{\bullet}OOCCl_3$
SPET				~0.00	99.92	41.59
SEPT				32.20		52.83
HT						
site 4a	14.56	100.00	100.00	8.53	0.08	2.55
site 7a	13.83			8.17		2.36
RAF						
site 1	14.56			8.53		0.67
site 2	2.38			8.49		
site 3	14.56			8.53		
site 4	14.25			8.53		
site 5	11.40			8.48		
site 6	14.46			8.53		

[a] At physiological pH (7.4).

a minor product, all of them are proposed to be formed in similar proportions. This is in line with the high reactivity, i.e., low selectivity, of this radical.

The presence of aqueous media dramatically changes the relative importance of the mechanisms of reaction. At physiological pH, the SEPT process becomes very important for both $^{\bullet}$OH and $^{\bullet}OOCCl_3$, accounting for 32.2% and 52.8% of the overall reactivity of sesamol toward these radicals. The SPET mechanism becomes the most important one for reaction with $^{\bullet}$OOH (99.9%), and it also significantly contributes to the overall reaction with $^{\bullet}OOCCl_3$ (41.6%). However, as we discussed above, the final product formed through both SPET and SEPT is the radical SO$^{\bullet}$. Therefore, the SO$^{\bullet}$ species is formed through three different channels of reaction: the direct HT from site 4a and from the SPET and the SEPT processes. Accordingly, it is estimated to represent ~41% and 97% of the formed products in the SOH reaction with $^{\bullet}$OH and $^{\bullet}OOCCl_3$, respectively, at physiological pH. This is in agreement with the estimations Joshi et al.,[20] who estimated these proportions to be 44% and 88%. As was the case in nonpolar environments, in aqueous solution reaction with $^{\bullet}$OH is predicted to produce a wide variety of products. In this case, all RAF channels are expected to be equally probable.

It should be noticed that for other systems it has been proposed that after OH adducts are formed elimination of a water molecule can occur, yielding a radical product that in our case would correspond to SO$^{\bullet}$.[74] It has also been demonstrated that solvent water molecules can assist this process, lowering the barriers of reactions. However, for the sesamol system, based on the experimental observations,[20] it can be concluded that since the adducts are observed they are stable enough and the dehydration process is not expected to play an important role.

UV−Vis Spectra. As mentioned in the Introduction, Joshi et al.[20] assigned two UV bands to the products formed by reactions of sesamol with free radicals. One of them, at 440 nm, was assigned to formation of SO$^{\bullet}$ and the other, at 350 nm, to a radical adduct, [SOH−OH]$^{\bullet}$. We computed the spectra of all the studied products to help understanding in detail the total spectra experimentally observed. For sesamol a band with an absorption maximum at 294[75] or 310[16] nm has been

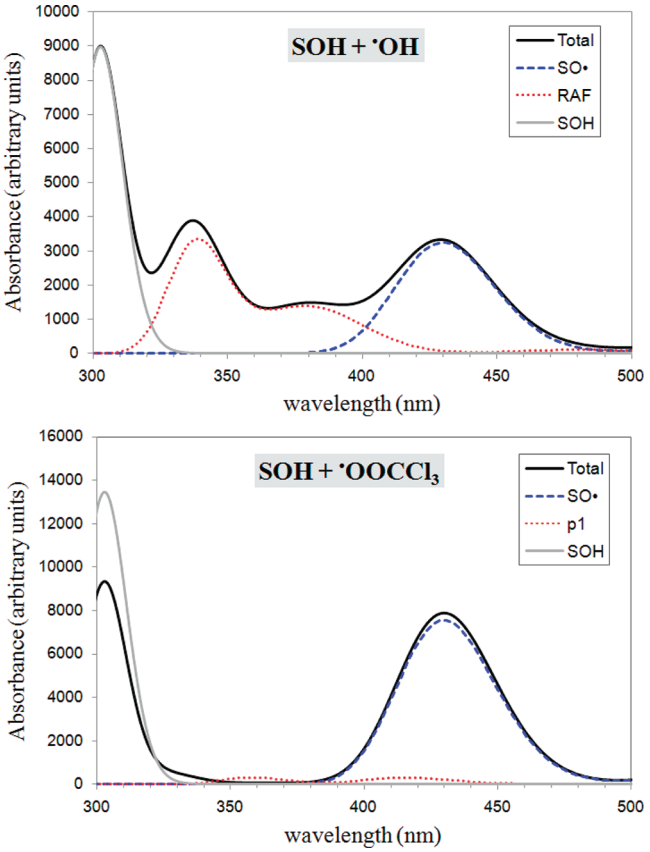

Figure 4. Computed UV−vis spectra: (A) for the SOH + $^{\bullet}$OH reaction and (B) for the SOH + $^{\bullet}OOCCl_3$ reaction. Gray line: sesamol.

identified. In the same region studied in the experiments, our computed spectrum of SOH shows a band at 251 nm, i.e., 51 nm lower than the average of the experimental values. Therefore, all computed spectra have been scaled accordingly to facilitate comparisons with experiments ($\lambda_{reported} = \lambda_{calculated} + 51$ nm). The spectra labeled as Total (Figure 4) were obtained using the additivity of absorbance and weighting the separated spectra according to the relative abundance of the formed products. The same strategy was used to obtain the spectrum labeled as RAF for the SOH + $^{\bullet}$OH reaction (Figure 4A). The separated spectra of all the radical adducts are provided as Supporting Information (Figure 2S).

The UV spectrum corresponding to the SOH + $^{\bullet}$OH reaction (Figure 4A) shows three bands. The band at ~300 nm was also observed in the experiments,[20] and as the figure shows it overlaps with the spectrum of sesamol. That is probably why it was not taken into account to characterize the evolution of the reaction. The other two bands appear at 428 and 338 nm, i.e., 12 nm lower with respect to the experimental data. The fist one arises because of the contribution of the spectrum of SO$^{\bullet}$ to the total spectrum and the second one because of the addition products formed through the RAF mechanism. The band around 350 is not present in the UV spectrum corresponding to the SOH + $^{\bullet}OOCCl_3$ reaction (Figure 4B) since, as discussed above, the RAF mechanism plays only a minor role in the overall reactivity of sesamol toward this radical. The band corresponding to SO$^{\bullet}$ appears at 431 nm in the calculated spectrum, i.e., only 9 nm lower than the experimental value. These results support the assignments proposed by Joshi et al.[20] Moreover, the good

agreement between the calculated and experimental wavelength values supports the reliability of the presented calculations.

Spontaneous deprotonation of the radical cation ($SOH^{\bullet+}$) to form $SO^{\bullet}$ was considered to weight the spectra show in Figure 4. To confirm this hypothesis the spectrum of $SOH^{\bullet+}$ was also computed (Figure 3S, Supporting Information). It presents two bands, one at 438 nm and another at 329 nm. The latter would appear in the same region (~350 nm) as that characteristic of the RAF products. Since for the SOH + $^{\bullet}OOCCl_3$ reaction $SOH^{\bullet+}$ would be the main product if it would not deprotonate to form $SO^{\bullet}$ and this band is not present in the experimental spectrum,[20] it can be concluded that our deprotonation hypothesis is correct. Therefore, SET is only a first step and the mechanism contributing the most to the overall reactivity of sesamol toward $^{\bullet}OOCCl_3$ is actually the sequential electron proton transfer.

CONCLUSIONS

Reactions of sesamol (SOH) with different free radicals, in lipid and aqueous media, have been studied. Five mechanisms of reaction have been considered: single electron transfer (SET), sequential electron proton transfer (SEPT), sequential proton electron transfer (SPET), hydrogen transfer (HT), and radical adduct formation (RAF). According to the overall rate coefficients, SOH is predicted to react about 1.6, 7339, and 110 times faster in aqueous solution than in nonpolar media, with $^{\bullet}OH$, $^{\bullet}OOH$, and $^{\bullet}OCCl_3$, respectively. The polarity of the environment not only increases the reactivity of sesamol toward free radicals but also dramatically changes the relative importance of the mechanisms of reactions studied in this work. The mechanism contributing the most to the overall reactivity of sesamol toward $^{\bullet}OOH$ and $^{\bullet}OOL$, in aqueous solution, is the sequential proton electron transfer (SPET), i.e., the SET from the anionic form of sesamol. Two main mechanisms were found for reaction of sesamol with $^{\bullet}OOCCl_3$, in aqueous solution, the SPET and SEPT, i.e., the SET from the neutral sesamol followed by deprotonation of the radical cation ($SOH^{\bullet+}$). Reaction with $^{\bullet}OH$ is predicted to produce a wide variety of products, regardless of the polarity of the environment. The anionic form of sesamol was found to be particularly reactive by transferring one electron to the studied free radicals. This mechanism was found to be responsible for the exceptional peroxyl radical scavenging activity of sesamol, which was found to be even better than carotenoids, 2-propenesulfenic acid, and glutathione under physiological conditions. The agreement between experimental and calculated rate constants and the UV data strongly support the mechanistic results provided in this manuscript. Moreover, this agreement also suggests that the methodology used in this work gives an excellent precision for relatively complex systems at reasonable computational costs.

ASSOCIATED CONTENT

Supporting Information. Gibbs free energies of activation ($\Delta G^{\ddagger}$) vs Gibbs free energies of reaction (ΔG) for different values of λ for the electron transfer reactions from SO^{-} to the studied free radicals; UV spectra of the products formed by the RAF mechanism in the SOH + $^{\bullet}OH$ reaction and of the radical cation of sesamol ($SOH^{\bullet+}$). This material is available free of charge via the Internet at http://pubs.acs.org.

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