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Theoretical and Experimental Studies of the Antioxidant and Antinitrosant Activity of Syringic Acid

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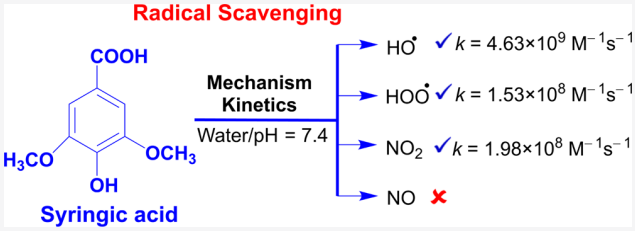
ABSTRACT: Syringic acid (SA) is a natural phenolic acid found in vegetables, fruits, and other plant-based foods. A range of biological activities were proposed for this compound including anticancer, antimicrobial, anti-inflammation, and anti-diabetic activities, as well as antioxidant and antinitrosant properties. In this study, the focus is on the latter two. The HO•, HOO•, NO, and NO_2 scavenging activities of SA were evaluated in physiological environments by kinetic and thermodynamic calculations. The computed rate constants of the HO• radical scavenging of SA were 4.63×10^9 and 9.77×10^7 M^{-1} s^{-1} in polar and nonpolar solvents, respectively. A comparison with the experimentally determined rate constant in aqueous solution yields a $k_{calculated}/k_{experimental}$ ratio of 0.3, thus the computed kinetic data are reasonably accurate. SA exhibited excellent HOO• and NO_2 scavenging activity in water ($k_{overall}(HOO^•) = 1.53 \times 10^8$ M^{-1} s^{-1} and $k_{overall}(NO_2) = 1.98 \times 10^8$ M^{-1} s^{-1}), whereas it did not show NO scavenging activity in any of the studied environments. In lipid medium, SA exhibited weak activity. Thus, in polar environments, the HOO• radical scavenging of SA is 1.53 times higher than that of ascorbic acid. Consistently, SA is a promising antioxidant and antinitrosant agent in polar environments.



1. INTRODUCTION

Syringic acid (SA, Figure 1) is a natural phenolic acid found in many vegetables, fruits, and spices, including pumpkin, olives, grapes, acai palm, red wine, rice, rye, wheat, oats, maize, barley, sorghum, sugar cane, and even honey.[1−5] SA is believed to have numerous beneficial biological activities including the protection of the brain, heart, and liver, as well as anticancer, antimicrobial, anti-inflammation, antidiabetic, anti-nitrosative, and antioxidant properties.[3] SA is also one of the main phenolics quantified in sugarcane molasses yielding up to 10 μg/g of dried extracts.[6,7] These sugarcane extracts exhibit strong antioxidant properties and beneficial actions consistent with those of SA, such as the improved regulation of the metabolic function and inflammation, in addition to antimicrobial and anti-cancer properties.[5,8] While these extracts contain several phenolics and other compounds, it is reasonable to attribute these actions in large part to the presence of SA. Because of the abundance of SA in a variety of food and medicinal plants, it is feasible to assume that it has been part of the ethnopharmacology practices of many cultures throughout history. However, information about SA in the modern context of nutritional and pharmacological practices is still lacking in the scientific literature.

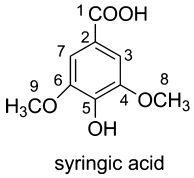


Figure 1. Structure of SA.

SA is a bioavailable polyphenol, with an absolute bioavailability of 86.27%.[9] Toxicology studies in rats demonstrated that SA had no detectable adverse effects.[10] The high bioavailability and low toxicity suggest that SA can be administered as a preventative measure against a range of diseases. Like for many polyphenols, the observed health benefits associated with SA have been mainly attributed to its antioxidant capacity.[4,5,11] However, other, more direct bioactivities are also reported. For example, preliminary studies indicated that SA may initiate post transcriptional epigenetic changes that have a potential protective effect against osteoporosis;[12] studies of both pure SA and extracts containing the compound in cell culture and animal models showed that it upregulated biochemical pathways, such as NRF-2, that are involved in the production of endogenous antioxidant compounds.[5,13] Nevertheless, antiox-

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idant activity is the best documented benefit of therapeutic administration of SA.

SA was identified as a potential natural antioxidant both in vivo and in vitro. SA exhibited good radical scavenging activity against β-carotene and 2,2-diphenyl-1-picrylhydrazyl (DPPH)[14] and presented high inhibition in total equivalent antioxidant capacity measurements.[15] Additionally, SA derivatives could prevent oxidative and carbonyl stress in the pathophysiology of atherosclerosis,[16] exhibit cell-mediated LDL oxidation, the cellular NADPH oxidase,[17] as well as the activity in phenolsulfotransferase involved in detoxification reactions.[18] However the mechanism and kinetics of the radical scavenging activity of SA have not been fully studied.

An often neglected activity of radical scavengers is the elimination of reactive nitrogen species (RNS), such as nitric oxide (NO) and nitric dioxide (NO_2), that are the main cause of nitrosative stress.[19−21] RNS and reactive oxygen species (ROS) are believed to damage membrane fatty acids, DNA, and protein structure.[22−24] It is suspected that SA can exert RNS-scavenging activity as well. Thus, a detailed evaluation of the overall activity and mechanism of SA in scavenging ROS and RNS is crucial to understand its biological role.

Previous works demonstrated that the mechanism and kinetics of radical reactions as well as the antioxidant capacity of organic compounds, particularly in the physiological environments, could be effectively and elegantly evaluated by the quantum chemistry calculations.[25−29] This study aims to apply this approach for investigating the overall radical scavenging potential of SA in aqueous and lipid media, by calculating the thermodynamic parameters responsible for such activity to identify the most likely radical scavenging mechanism and by evaluating the kinetics of the $HO^•$, $HOO^•$, NO, and NO_2 scavenging reactions to estimate the activity of SA. To validate SA as an antioxidant and to benchmark the computational results, the experiments are also performed by standard radical scavenging assays.

2. RESULTS AND DISCUSSION

2.1. ABTS and DPPH Antioxidant Assays. To validate SA as a potential antioxidant and to serve as a benchmark for the computational results, the antioxidant activity of SA was evaluated by 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and DPPH assays carried out in aqueous solution at pH = 7.4. Ascorbic acid (AA) was used as a reference and the results are presented in Table 1. It was found that SA (IC_{50}(SA) = 21.06 ± 8.33 μmol/mL) exhibited substantially higher $ABTS^{•+}$ scavenging activity than AA (IC_{50}(AA) = 57.19 ± 4.57 μmol/mL) under the studied conditions. The IC_{50}(SA) value of the DPPH assays was also slightly higher than that of AA. The difference may be related to the differences in the antioxidant mechanism between SA and AA. It was shown that the radical scavenging of AA in polar medium at pH 7.4 is defined by the formal hydrogen transfer (FHT) mechanism.[26] Because the DPPH assay is optimized for a H-abstraction scavenger,[30,31] the assay could potentially favor AA in the case SA follows a different radical scavenging pathway.

Table 1. IC_{50} Values for ABTS and DPPH Assays for SA and AA

	ABTS IC_{50} (μmol/mL)	SD	DPPH IC_{50} (μmol/mL)	SD
SA	21.06	8.33	88.16	7.84
AA	57.19	4.57	64.56	1.38

2.2. Thermodynamic Study. *2.2.1. Acid−Base Equilibria.* A previous study showed that the pK_a values of the two-step dissociation of SA were pK_{a1} = 4.20 (COO−H) and pK_{a2} = 9.00 (O5−H).[32] Thus, under physiological conditions (pH 7.40), SA co-exists in a monovalent (SAA, 97.5%) and a divalent anionic state (SAA-O5, 2.5%) and these forms were used to evaluate the radical scavenging of SA in aqueous solution. In the lipid environment, the neutral SA was modeled.

In this study, three main antioxidant pathways, including single electron transfer (SET), FHT, and radical adduct formation (RAF),[33−35] were considered to assess the reactivity of SA toward $R^•$ (R = $HO^•$ and $HOO^•$) radicals and nitrogen oxides (NO, NO_2) in the two solvents following the literature.[22,36,37]

2.2.2. Mechanism Evaluation. In the initial step, bond dissociation energy (BDE) values were calculated (Table 2) to evaluate the radical scavenging of SA following the FHT mechanism. As shown in Table 1, the lowest BDE value was observed at the O5 position with BDEs = 81.0 and 83.9 kcal/mol in water (W) and pentyl ethanoate (PE) solvents, respectively, whereas those for other positions were higher at about 98.6−115.7 kcal/mol. This suggests that the radical scavenging of SA following the FHT mechanism proceeds by H-abstraction at the O5−H bond, and thus, this position was used to investigate the antioxidant activity of SA following FHT mechanism.

Table 2. Calculated BDE Values (in kcal/mol) of SA in the Studied Solvents

	BDE	
position	W	PE
C3	115.3	115.7
C8	100.0	98.6
O1		109.1
O5	81.0	83.9

The ΔG^o values were calculated for the SA + $R^•$ ($HO^•$, $HOO^•$) or NO_x (NO, NO_2) reactions following each mechanisms (SET, FHT, and RAF, Table S1, Supporting Information); the results are presented in Table 3. The data show that the hydroxyl radical scavenging of SA is almost always spontaneous (ΔG <0) in the studied media, with the exception of the SET mechanism in the PE solvent. However, the reactions of SA with $HOO^•$ or NO_2 in the aqueous solution were only spontaneous following the SET (for SAA-O5 state) and FHT (for the O5−H bond of SAA) mechanisms, whereas in the nonpolar solvent, negative ΔG^o values were only observed for $HOO^•$ radical scavenging, following the FHT mechanism. The SA + NO reaction was not spontaneous for any of the studied environments and mechanisms, particularly in the RAF pathway, where even the products could not to be formed correctly. Consistently, NO scavenging does not occur with SA. It was suggested recently that NO is a relatively stable radical and that its role in causing nitrosative damage is because of a downstream effect after its oxidation,[21] that is consistent with our results.

2.3. Kinetic Study. Based on the above results, the $k_{overall}$ for the $HO^•$, $HOO^•$, and NO_2 scavenging of SA was calculated according to the following equations.

In aqueous solution

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Table 3. Calculated ΔG° Values of the Reactions of SA with $HO^{\bullet}$, $HOO^{\bullet}$, NO, and NO_2 in Water (W) and PE Solvents (in kcal/mol), at 298.15 K

mechanism		$OH^{\bullet}$		$OOH^{\bullet}$		NO		NO_2	
		W	PE	W	PE	W	PE	W	PE
SET	SAA-O5	−25.3		−2.3		54.1		−23.3	
	SAA/SA	4.9	55.6	27.9	104.8	84.3	119.2	6.9	45.4
FHT	O5	−40.7	−33.3	−8.1	−0.2	29.8	36.0	−5.3	4.3
RAF	C2	−8.6	−2.9	18.3	63.2			27.0	31.9
	C3	−8.7	−9.1	19.1	56.5			25.4	25.1
	C4	−10.6	−10.7	18.5	21.5			28.7	31.7
	C5	−18.3	−18.6	12.2	13.6			21.6	24.4

Table 4. Gibbs Free Energies of Activation ($\Delta G^{\neq}$, kcal/mol), Tunneling Corrections (κ), Nuclear Reorganization Energy (λ, kcal/mol), Rate Constants (k_{app}, M^{-1} s^{-1}), and Branching Ratios (Γ, %) at 298.15 K, in the SA Oxidation by $HO^{\bullet}$ Radicals in Water and PE Solvents

mechanism		W				PE			
		$\Delta G^{\neq}$	κ	k_{app}	Γ	$\Delta G^{\neq}$	κ	k_{app}	Γ
SET	SAA-O5	19.5	5.2[a]	3.40×10^{-2}	0.0				
	SAA	4.9	5.2[a]	1.40×10^{9}	29.5				
FHT	O5	6.2	1.0	1.90×10^{8}	4.0	8.5	4.6	1.60×10^{7}	16.4
RAF	C2	6.7	1.2	8.70×10^{7}	1.8	9.8	1.2	4.60×10^{5}	0.5
	C3	5.2	1.1	7.10×10^{8}	15.0	8.5	1.2	3.90×10^{6}	4.0
	C4	6.2	1.0	1.60×10^{8}	3.4	10.0	1.2	3.30×10^{5}	0.3
	C5	3.8	1.0	2.20×10^{9}	46.3	6.7	1.1	7.70×10^{7}	78.8
$k_{overall}$				**4.63×10^{9}**				**9.77×10^{7}**	

[a]The nuclear reorganization energy (λ).

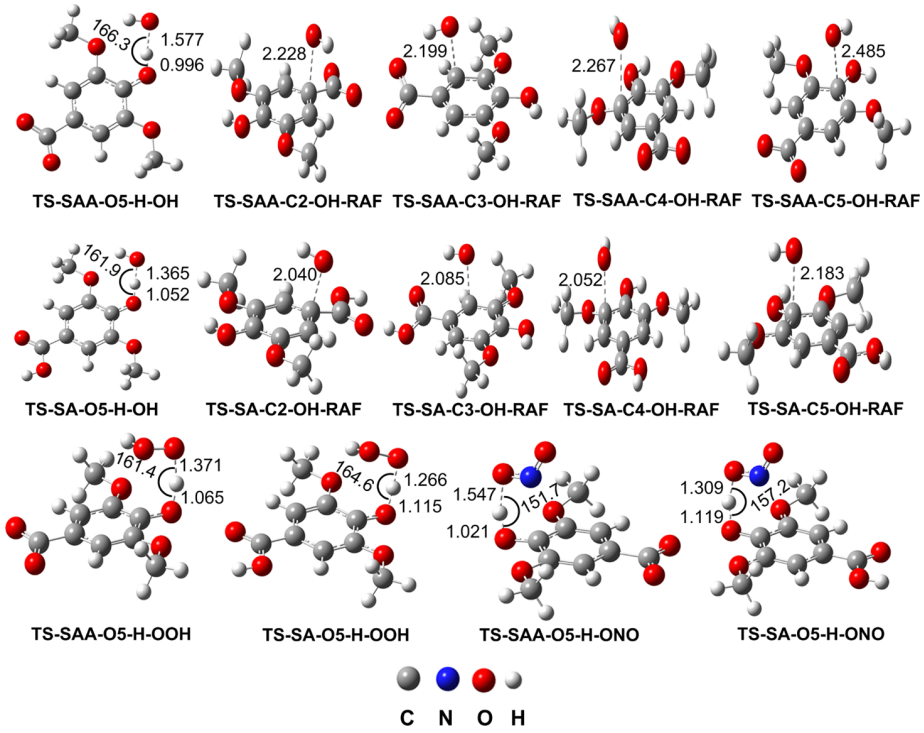

Figure 2. Optimized geometries TSs between SA and $HO^{\bullet}$, $HOO^{\bullet}$, and NO_2 in the studied environments following the FHT and RAF mechanism.

$$k_{overall}(OH) = 0.025k_{SET}(SAA\text{-}O5) + 0.975\left(k_{SET}(SAA) + \sum k_{RAF}(SAA) + \sum k_{FHT}(SAA)\right) \quad (1)$$

$$k_{overall}(OOH) = 0.025k_{SET}(SAA\text{-}O5) + 0.975k_{FHT}(SAA) \quad (2)$$

$$k_{overall}(NO_2) = 0.025k_{SET}(SAA\text{-}O5) + 0.975k_{FHT}(SAA) \quad (3)$$

In nonpolar solvent

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Table 5. $\Delta G^{\neq}$ (kcal/mol), the Nuclear Reorganization Energy (λ, kcal/mol), Tunneling Corrections (κ), and k_{app} (M^{-1} s^{-1}) of the HOO• and NO_2 Scavenging of SA

		OOH						NO_2					
		W			PE			W			PE		
mechanism		$\Delta G^{\neq}$	κ	k_{app}	$\Delta G^{\neq}$	κ	k_{app}	$\Delta G^{\neq}$	κ	k_{app}	$\Delta G^{\neq}$	κ	k_{app}
SET	SAA-O5	3.2	17.1[a]	6.10×10^9				0.4	30.5[a]	7.90×10^9			
	SAA							11.4	30.4[a]	2.60×10^4			
FHT	O5	16.8	127.2	4.10×10^2	19.3	132.1	5.3	17.0	1.2	2.5	18.2	3.4	0.9
$k_{overall}$				**1.53×10^8**			**5.3**			**1.98×10^8**			**0.9**

[a]The nuclear reorganization energy (λ).

$$k_{overall}(OH) = \sum k_{RAF}(SA) + \sum k_{FHT}(SA) \quad (4)$$

$$k_{overall}(OOH) = k_{FHT}(SA) \quad (5)$$

$$k_{overall}(NO_2) = k_{FHT}(SA) \quad (6)$$

2.3.1. Hydroxyl Radical Scavenging Activity of SA. Calculations for the $k_{overall}$ of the HO• radical scavenging reaction were carried out following the eqs 1 and 4. The kinetic results and the optimized transition state (TS) structures are presented in Table 4 and Figure 2, respectively. It was found that the $k_{overall}$ for the aqueous solution ($k_{overall} = 4.63 \times 10^9$ M^{-1} s^{-1}) was about 47 times higher than that for the nonpolar medium ($k_{overall} = 9.77 \times 10^7$ M^{-1} s^{-1}). A comparison with the experimental rate constant in aqueous solution ($k = 1.6 \times 10^{10}$ M^{-1} s^{-1})[38] yields a $k_{calculated}/k_{experimental}$ ratio of 0.3, thus the computed kinetic data are reasonably accurate. The RAF mechanism played an important role in the HO• radical scavenging activity of SA in all of the studied media ($\Gamma > 66.5\%$), whereas the FHT mechanism contributed only 16.4 and 4.0% of the $k_{overall}$ in the PE and W solvents, respectively. The contribution of the SET mechanism in the $k_{overall}$ in a polar environment was about 29.5%. Thus, the results demonstrate that the SET and RAF pathways decide the HO• radical scavenging of SA in the aqueous solution, and the RAF mechanism in the lipid medium. The HO• antiradical activity of SA is fairly lower than that of typical antioxidants such as edaravone,[39] melatonin,[40] sesamol[40] dopamine,[41] indole-3-carbinol,[36] and ramalin[37] in all of the studied media. Thus, SA is a moderately active hydroxyl radical scavenger.

2.3.2. HOO• and NO_2 Scavenging Activity of SA. The kinetic calculations for the HOO• and NO_2 scavenging of SA were performed, following the eqs 2, 3, 5, and 6. The kinetic results are presented in Table 5, whereas the optimized TS structures are shown in Figure 2. As shown in Table 5, the HOO• and NO_2 scavenging of SA ($k_{overall}(HOO) = 1.53 \times 10^8$ M^{-1} s^{-1} and $k_{overall}(NO_2) = 1.98 \times 10^8$ M^{-1} s^{-1}) in the aqueous solution is about 10^8 times higher than in the lipid medium ($k_{overall} = 5.3$ and 0.9 M^{-1} s^{-1}, respectively). The SET mechanism dominated the HOO• and NO_2 scavenging activity of SA in the polar environment. It was interesting that the dianion state (SAA-O5) played an important role in the radical scavenging of SA in water, despite the fact that the presence of this state is minor (2.5%) in the aqueous solution at pH 7.40. Comparing the obtained results with AA ($k = 9.97 \times 10^7$ M^{-1} s^{-1}),[26] the HOO• radical scavenging activity of SA is 1.53 times higher. At the same time, the NO_2 scavenging activity of SA is about 66 times higher than that of tryptophan ($k = 3.00 \times 10^6$ M^{-1} s^{-1})[21] in aqueous solution. Thus, SA is a promising HOO• and NO_2 scavenger in polar environments.

3. CONCLUSIONS

The HO•, HOO•, NO and NO_2 scavenging activity of SA was investigated by kinetic and thermodynamic calculations. It was found that SA had low NO scavenging in all of the studied environments, whereas it exhibited hydroxyl radical scavenging with $k_{overall} = 4.63 \times 10^9$ and 9.77×10^7 M^{-1} s^{-1} in polar and nonpolar solvents, respectively. The RAF and SET mechanisms decide the HO• antiradical activity of SA in aqueous solution and the RAF mechanism in the lipid medium. The HOO• and NO_2 scavenging of SA in aqueous solution ($k_{overall}(HOO) = 1.53 \times 10^8$ M^{-1} s^{-1} and $k_{overall}(NO_2) = 1.98 \times 10^8$ M^{-1} s^{-1}) is about 10^8 times higher than that for the lipid medium. Compared with AA, the HOO• radical scavenging of SA is 1.53 times higher. The $ABST^{\bullet+}$ and DPPH assays also confirmed that SA could exhibit radical scavenging activity as high as AA in aqueous solution at pH 7.4. Thus, SA is a good antioxidant in polar environments.

4. COMPUTATIONAL AND EXPERIMENTAL METHODS

4.1. Computational Method. Our methodology has been validated in a range of former works.[35−37] Briefly, the thermochemical properties and the kinetics of representative radical scavenging reactions were computed following the M05-2X/6-311++G(d,p) method.[25,26,35,42] Analysis of the thermochemical parameters is used to identify the most likely radical scavenging reaction pathway, which is then used in the kinetic calculations. The quantum mechanics based test for the overall free radical scavenging activity protocol,[25,26,36,43−45] with the solvation model density (SMD)[46]—water for the polar environment and PE for the nonpolar environment—were used to perform the kinetic calculations. This method has been benchmarked against experimental data and has demonstrably low errors (k_{calc}/k_{exp} ratio = 1−2.9), particularly in lipid and aqueous solutions,[25,26,35,43] and widely used to calculate rate constants for the radical scavenging in both nonpolar and polar environments.[25,27,35,47−49]

Rate constants (k) were computed following the TS theory and 1 M standard state at 298.15 K according to the eq 7[36,50−54]

$$k = \sigma\kappa\frac{k_B T}{h}e^{-(\Delta G^{\neq})/RT} \quad (7)$$

where σ is the reaction symmetry number,[55,56] κ contains tunneling corrections calculated using an Eckart barrier,[57] k_B is the Boltzmann constant, h is the Planck constant, and $\Delta G^{\neq}$ is the Gibbs free energy of activation.

The Marcus theory was used to estimate the reaction barriers of SET reactions.[58,59] The free energy of reaction $\Delta G^{\neq}$ for the SET pathway was computed following the eqs 8 and 9.

$$\Delta G_{SET}^{\neq} = \frac{\lambda}{4}\left(1 + \frac{\Delta G_{SET}^{0}}{\lambda}\right)^2 \quad (8)$$

$$\lambda \approx \Delta E_{SET} - \Delta G_{SET}^{0} \quad (9)$$

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where ΔG_{SET} is the Gibbs energy of the reaction, ΔE_{SET} is the nonadiabatic energy difference between reactants and vertical products for SET.[60,61]

For rate constants that were close to the diffusion limit, a correction was applied to yield realistic results.[26] The apparent rate constants (k_{app}) were calculated following the Collins−Kimball theory in the solvents at 298.15 K;[62] the steady-state Smoluchowski rate constant (k_D) for an irreversible bimolecular diffusion-controlled reaction was calculated following the literature corresponding to eqs 10 and 11.[26,63]

$$k_{app} = \frac{k_{TST}k_D}{k_{TST} + k_D} \tag{10}$$

$$k_D = 4\pi R_{AB} D_{AB} N_A \tag{11}$$

where R_{AB} is the reaction distance, N_A is the Avogadro constant, and $D_{AB} = D_A + D_B$ (D_{AB} is the mutual diffusion coefficient of the reactants A and B),[62,64] where D_A or D_B is estimated using the Stokes−Einstein formulation 12.[65,66]

$$D_{A\text{ or }B} = \frac{k_B T}{6\pi\eta a_{A\text{ or }B}} \tag{12}$$

η is the viscosity of the solvents (i.e., $\eta(H_2O) = 8.91 \times 10^{-4}$ Pa s, η(PE) $= 8.62 \times 10^{-4}$ Pa s) and a is the radius of the solute.

The solvent cage effects were included following the corrections proposed by Okuno,[67] adjusted with the free volume theory according to the Benson correction[26,41,68,69] to reduce over-penalizing entropy losses in solution. For the species that have multiple conformers, all of these were investigated and the conformer with the lowest electronic energy was included in the analysis.[35,37] The hindered internal rotation treatment was also applied to the single bonds to ensure that the obtained conformer has the lowest electronic energy.[37,70] All TSs were characterized by the existence of only one single imaginary frequency. Intrinsic coordinate calculations were performed to ensure that each TS is connected correctly with the precomplex and postcomplex. All of the calculations were performed with the Gaussian 16 suite of programs.[71]

4.2. ABTS Assay. The ABTS assay was conducted by the modified method of Re et al.[72] Briefly, 7 mM ABTS ammonium was dissolved in water and mixed with 2.45 mM potassium persulfate. The mixture was allowed to stand at room temperature for 16 h in the dark to produce $ABTS^{\bullet+}$. The $ABTS^{\bullet+}$ solution and samples were then diluted with 50 mM pH 7.4 phosphate buffer. After addition of 100 μL of diluted $ABTS^{\bullet+}$ to 100 μL of sample dilutions in a well of a 96-well microplate and incubated for 30 min at 26 °C. The A_{734} absorbance was measured using a Victor NIVO Multimode plate reader (PerkinElmer). Dilutions of compounds were assayed in triplicate and were used to generate a standard curve. IC_{50} for each compound was determined by regression analysis.

4.3. DPPH Assay. The DPPH assay was conducted based on the methods reported by Brand-Williams et al.[73] Briefly, a 2.9 mM solution of DPPH was prepared in ethanol. Compounds were diluted in 50 mM pH 7.4 phosphate buffer. The diluted compound (100 μL) was mixed with 100 μL of the DPPH reagent solution in a 96-well microplate and incubated for 30 min. The A_{517} nm absorbance was measured using a Victor NIVO Multimode plate reader (PerkinElmer). Dilutions of compounds were assayed in triplicate and were used to generate a standard curve. IC_{50} for each compound was determined by regression analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02258.

Cartesian coordinates and the energies of all of the compounds, radicals, anions, anion−radicals, radical−cations, precomplexes, TSs, postcomplexes, and products in the studied environments (PDF)

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Notes

The authors declare no competing financial interest.

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