THE JOURNAL OF PHYSICAL CHEMISTRY B

ARTICLE

pubs.acs.org/JPCB

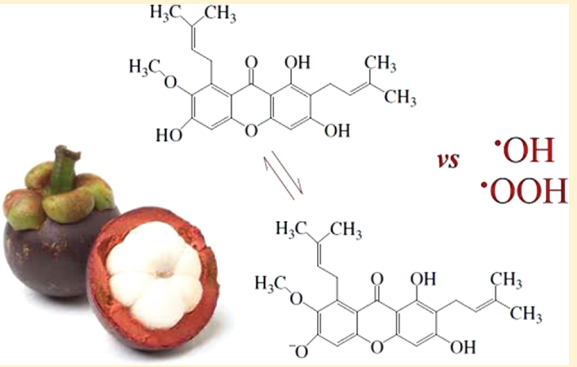
Free Radical Scavenger Properties of α-Mangostin: Thermodynamics and Kinetics of HAT and RAF Mechanisms

Ana Martínez,*,† Annia Galano,‡ and Rubicelia Vargas‡

†Departamento de Materia Condensada y Criogenia, Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, Circuito Exterior S. N., Ciudad Universitaria, CP 04510, México D. F.

‡Departamento de Química, Universidad Autónoma Metropolitana-Iztapalapa, San Rafael Atlixco 186, Col. Vicentina, Iztapalapa, CP 09340, México D. F.

ABSTRACT: Mangosteen is a tropical fruit that presents beneficial effects on human health since it is rich in anthocyanins and xanthones, which are considered bioactive compounds that have been described as good free radical scavengers. One of its most active compounds is α-mangostin. In this report, a theoretical study on the free radical scavenger capacity of α-mangostin and its monoanion is analyzed using the density functional theory approximation. Two well-known reaction mechanisms are investigated: the hydrogen atom transfer (HAT) and the radical adduct formation (RAF). Two other mechanisms are also considered: sequential electron proton Transfer (SEPT) and proton coupled electron transfer (PCET). According to thermodynamics and kinetics, α-mangostin and its deprotonated form are good free radical scavenger through the HAT mechanism, with the anionic (deprotonated) form being more reactive than the neutral one. Their capacity to scavenge OOH free radical is similar to that of carotenes, higher than that of allicin, much higher than that of melatonin and *N*-acetylcysteine amide, and about 15 times lower than that of 2-propenesulfenic acid.



1. INTRODUCTION

Mangosteen (*Garcinia mangostana* Linn)[1] is considered the queen of the tropical fruits in South East Asia not only for its appearance and flavor but also for its beneficial effects on human health.[2−11] It is rich in anthocyanins and xanthones, which are considered bioactive compounds that have been described as good free radical scavengers.[12,13] This is important because over the past two decades a number of theoretical and experimental investigations have contributed to build the consensus that diets rich in substances that act as good free radical scavengers (antioxidants or antiradicals) have beneficial effects on human health.[14,15]

Xanthones, the major secondary metabolites of mangosteen, have been reported as antimycobacterials,[4] antifungals,[5] and antioxidants.[2,3,10] Particularly, xanthones as antioxidants have become the focus of numerous investigations since they are important components of the human diet. For this reason, several xanthones have been studied in order to determine their capacity as free radical scavengers. For α-mangostin, the first xanthone isolated from the mangosteen fruit,[16] there is a recent report that experimentally supports its capacity to deactivate singlet oxygen, superoxide anion, and peroxynitrite anion in a concentration-dependent way but also its incapacity to scavenge hydroxyl radicals and hydrogen peroxide.[10]

Since the free radical scavenging properties are apparently very important for human health, it is vital to analyze the viable mechanism for each substance on the face of its antiradical properties. In spite of the existence of different experimental results concerning the antioxidant capacity of xanthones, there are no theoretical investigations analyzing the free radical scavenger capacity of these molecules nor determining the reaction mechanisms. Thus the main goal of this work is to study the reaction of α-mangostin with two important free radicals (•OH and •OOH). Notwithstanding that several mechanisms are discussed in the literature[13,17−27] referring to the reactions of free radicals (R•) with several antiradical (anti) substances, in this work we considered specifically two mechanisms for α-mangostin (Figure 1):

hydrogenatomtransfer (HAT):

$$R^{\bullet} + \text{anti} \rightarrow RH + \text{anti}_{(-H)}^{\bullet} \quad (I)$$

radicaladductformation (HAT):

$$R^{\bullet} + \text{anti} \rightarrow \text{R-anti}^{\bullet} \quad (II)$$

For these two mechanisms, the adiabatic Gibbs free energies and the kinetic parameters are reported. To properly asses the antioxidant activity of α-mangostin, the ionic form must be considered since according to its most acidic *p*Ka value (7.22 ± 0.20),[28] under physiological conditions (pH 7.4) 39.8% of

Received: June 4, 2011
Revised: September 16, 2011
Published: September 21, 2011

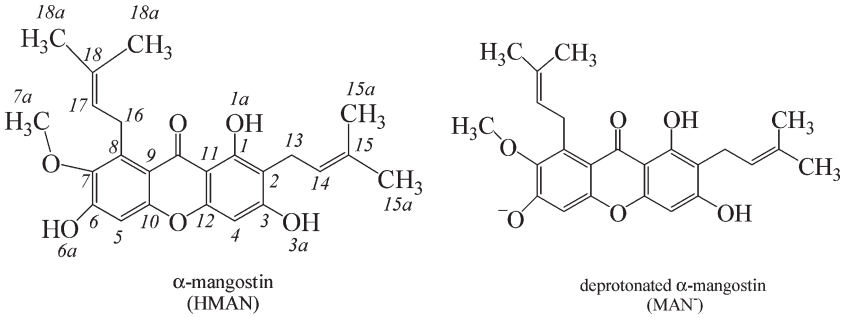


Figure 1. Antiradical molecules studied in this work. Italic numbers identify the numbering for hydrogen atoms.

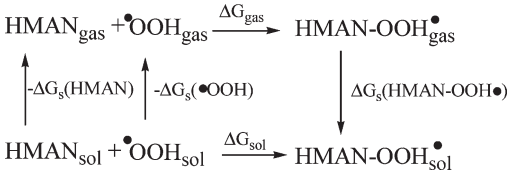
mangostin would be as the neutral form and 60.2% as the monoanionic form. The discussion about the adiabatic Gibbs free energies and the kinetic parameters are included for α-mangostin (HMAN) and also for deprotonated α-mangostin (MAN^-) (Figure 1). Additionally, an analysis of the sequential electron proton transfer (SEPT) and proton coupled electron transfer (PCET) mechanisms is reported.

2. COMPUTATIONAL DETAILS

Geometry optimizations and frequency calculations have been carried out using the BPW91 functional and the 6-31+G(d,p) basis set. The electronic energies were improved by single point calculations using the 6-311+G(d,p) basis set. 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). Intrinsic reaction coordinate (IRC) calculations have been performed to confirm that the transition states properly connect reactants and products. All the electronic calculations were performed with Gaussian 03 package of programs.[29] For the HAT mechanism, eight hydrogen atoms were considered (1a, 3a, 6a, 7a, 13, 15a, 16, and 18a, Figure 1) to produce α-mangostin and deprotonated α-mangostin both without one hydrogen atom: $[HMAN_{(-H)}]^\bullet$ and $[MAN_{(-H)}{}^-]^\bullet$, respectively. The radical addition was model in every carbon atom with double bonds (the exceptions are C13 and C16).

Thermodynamic corrections at 298.15 K were included in the calculation of relative energies. The stationary points were first modeled in gas phase (vacuum), and solvent effects were included a posteriori by single point calculations using the polarizable continuum model (PCM), specifically the integral-equation-formalism (IEF-PCM)[30−32] and RADII = UAHF, with the option SCFVAC at HF/6-31G(d,p) level of theory, as recommended by Gaussian's manual for computing solvation free energies. They have been performed using benzene and water as solvents, to mimic nonpolar and polar environments, respectively. This approach has been successfully used before for describing radical-molecule reactions in solution involved in the antioxidant activity of different compound.[22−27]

Relative Gibbs free energies in solution have been computed using thermodynamic cycles and the Hess law, explicitly including solvation free energies. For example for •OOH additions to α-mangostin (HMAN):



Within this strategy the Gibbs free energy of reaction in solution (ΔG_{sol}) can be obtained as the sum of the Gibbs free energy of reaction in vacuum (ΔG_{gas}) and the difference in solvation free energies ($\Delta\Delta G_s$)

$$\Delta G_{sol} = \Delta G_{gas} + \Delta\Delta G_s \quad (1)$$

where $\Delta\Delta G_s$ is calculated as

$$\Delta\Delta G_s = \Delta G_s(HMAN - OOH^\bullet) - \Delta G_s(HMAN) - \Delta G_s(^\bullet OOH) \quad (2)$$

with ΔG_s representing the free energies of solvation. In all cases, the reference state is 1 M. The solvent cage effects have been included according to the corrections proposed by Okuno,[33] taking into account the free volume theory.[34] These corrections are in good agreement with those independently obtained by Ardura et al.[35] and have been successfully used before.[36−38]

Since DFT calculations for obtaining dissociation energies of anions are significantly affected by self-interaction error, some test calculations were done employing M05-2X functional (that is reported as free of self-interaction error) and similar results were obtained.

The rate constants (k) were calculated using conventional transition state theory (TST)[39−41] and 1 M standard state as

$$k = \sigma\kappa \frac{k_B T}{h} e^{-(\Delta G^\ddagger)/RT} \quad (3)$$

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 Eckart barrier.[42] TST has been recently proven to be enough for properly describing chemical reactions between free radicals and anitoxidants.[26]

The kinetics investigation started searching for the transition states (TS) at BPW91/6-31+G(d,p) level of theory. However every attempt to locate the TS involved in the H transfer from the O3a site of MAN^- was unsuccessful. In addition we found convergence issues for the single point calculation of the TS corresponding to the H transfer from site 15a MAN^-, at BPW91/6-311+G(d,p) level of theory. Therefore we decided to perform the kinetic study of the HMAN/MAN^- + •OOH reactions with a different functional. We have chosen the M05-2X functional to that purpose. This functional was chosen because it has been recommended for kinetic calculations by their developers,[43] and it has been also successfully used by independent authors.[44−49]

Table 1. Gibbs Free Energies of HAT Reaction (kcal/mol) of α-Mangostin with •OH and •OOH in Water and Benzene Solutions

	•OH + HMAN → H_2O + $[HMAN_{(-H)}]^{\bullet}$		•OOH + HMAN → H_2O_2 + $[HMAN_{(-H)}]^{\bullet}$	
H number	G water	G benzene	G water	G benzene
1a	−27.58	−24.41	5.06	11.46
3a	−31.68	−30.32	0.96	5.55
6a	−37.10	−41.31	−4.46	−5.44
7a	−25.62	−24.66	7.02	11.21
13	−44.92	−44.03	−12.28	−8.16
15a	−34.42	−33.3	−1.78	2.57
16	−45.71	−44.63	−13.07	−8.76
18a	−34.84	−33.66	−2.20	2.21

Moreover, the reliability of the kinetic data obtained with this functional, for radical−molecule reactions, has been proven before by comparison with experimental data.[45]

3. RESULTS AND DISCUSSION

3.1. Thermodynamics. *Hydrogen Atom Transfer (HAT) Mechanism.* The adiabatic Gibbs free energies were obtained in benzene and water solutions, considering hydrogen atoms at different positions of α-mangostin for the dissociation (see Computational Details). The results are shown in Table 1. As can be seen, for •OH all the reactions are exergonic both in water and benzene. According to these results, the HAT reaction of this free radical with α-mangostin is thermodynamically feasible for all the hydrogen atoms considered in this investigation. As a consequence, α-mangostin is able to scavenge this free radical through this mechanism. The results with •OOH indicate that most of the reactions in water are exergonic, and the exceptions are H transfers from sites 1a, 3a, and 7a. In benzene solution the exergonic reactions are from sites 6a, 13, and 16. This indicates that the HAT reaction of α-mangostin with •OOH is thermodynamically feasible for some hydrogen atoms, and therefore, this molecule is also able to scavenge this free radical. Since not all of the hydrogen atoms are "reactive" toward this mechanism, it can be considered that to scavenge •OOH, α-mangostin is not as good as it is to deactivate •OH. This is a logical finding since •OH is known to be more reactive than •OOH.

The HAT reaction of deprotonated α-mangostin (MAN^-) was also analyzed. It can be expected that this species exists in water under physiological conditions, but not in nonpolar environments. For this reason, in this case the analysis was done only for aqueous solution. The results reported in Table 2 indicate that the reaction is exergonic in most of the cases. It is endergonic for the reaction with •OOH when hydrogens at positions 1a and 7a are involved. Apparently, the H atoms at these sites are the less reactive within this molecule. In view of these results, it can be concluded that α-mangostin and deprotonated α-mangostin are able (thermodynamically) to scavenge •OH and •OOH.

Radical Adduct Formation (RAF) Mechanism. For the addition of •OH and •OOH at different double C−C bonds of α-mangostin, the adiabatic Gibbs free energies were also obtained in benzene and water solutions. The results are shown in Table 3. For •OH most of the reactions are exergonic both in polar and nonpolar environments. Only the radical additions to C9 and C11 are endergonic. However, for •OOH none of the RAF reactions is thermochemically viable. As well, there are also some •OOH-HMAN products that are not formed (indicated with *a* in Table 3). With these results, it is possible to conclude that the RAF mechanism is not thermodynamically feasible for α-mangostin to scavenge •OOH. In order to scavenge this free radical, the RAF mechanism is not a possibility for α-mangostin.

Table 2. Gibbs Free Energies of HAT Reaction (kcal/mol) of Deprotonated α-Mangostin (MAN^-) with •OH and •OOH in Water Solutions

	•OH + MAN^- → H_2O + $[MAN^-_{(-H)}]^{\bullet}$	•OOH + MAN^- → H_2O_2 + $[MAN^-_{(-H)}]^{\bullet}$
H number	G water	G water
1a	−31.9	0.78
3a	−35.4	−2.79
7a	−25.84	7.03
13	−46.36	−13.99
15a	−36.19	−3.55
16	−47.25	−14.61
18a	−37.15	−4.51

Similar results were found for deprotonated α-mangostin (see Table 4). With •OH, the reaction is exergonic in most of the cases, being the exceptions C9, C10, C11, and C12. These carbon atoms that are at the middle of two benzene like rings, apparently are not very reactive. The most reactive carbon atoms are C8, C14, C15, C17, and C18, probably because these carbon atoms present lower steric impediments. Whatever the case, RAF mechanism is viable to scavenge •OH but not •OOH. Due the higher reactivity of •OH this is a reasonable result.

It was previously reported the experimental incapacity of α-mangostin to scavenge hydroxyl radicals and hydrogen peroxide.[10] The results reported here are in general in agreement with these experiments but are in contradiction with the idea that •OH is not reactive toward α-mangostin. According with these theoretical results, the reaction is very exergonic, so it is thermodynamically feasible. More experiments would be necessary in order to investigate if the very highly reactive •OH does not react with a very reactive radical scavenger as α-mangostin, or if there is another explanation to the lack of reactivity reported before.[10]

3.2. Kinetics. The channels of reaction described as endergonic have been ruled out as relevant to the scavenging activity of HMAN/MAN^-. 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 with other chemical species. 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. However, this work focuses only on the first step of the oxidation of HMAN/MAN^- by •OH and •OOH. Therefore the kinetic calculations have been performed only for those channels described as exergonic.

The fully optimized geometries of the transition states involved in the reaction channels identified as exergonic are shown in Figure 2. Hydrogen bond interactions between the H atom in the OOH radical and one of the O atoms in HMAN were found for all TSs corresponding to reaction channels involving H

Table 3. Gibbs Free Energies of RAF Reaction (kcal/mol) of α-Mangostin with •OH and •OOH in Water and Benzene Solutions

	•OH +HMAN → •OH-HMAN		•OOH +HMAN → •OOH-HMAN	
C number	G benzene	G water	G benzene	G water
C1	−3.88	−2.95	28.32	20.23
C2	−8.55	−6.10	22.25	14.14
C3	−4.26	−3.24	*a*	*a*
C4	−7.48	−11.04	*a*	*a*
C5	−10.75	−10.41	19.51	19.38
C6	−12.10	−9.14	*a*	*a*
C7	−12.17	−10.89	*a*	*a*
C8	−15.30	−11.74	22.58	27.59
C9	1.44	2.12	31.78	32.58
C10	−8.92	−6.21	24.19	25.35
C11	2.20	1.74	*a*	*a*
C12	−6.65	−4.18	25.45	25.80
C14	−24.29	−24.45	14.30	13.06
C15	−20.34	−19.74	10.64	10.93
C17	−21.76	−19.68	9.22	11.22
C18	−20.66	−18.24	8.15	11.00

[a] Products are not formed. •OOH remains dissociated from HMAN.

Table 4. Gibbs Free Energies of RAF Reaction (kcal/mol) of Deprotonated α-Mangostin (MAN^-) with •OH and •OOH in Water Solutions

	•OH + MAN^- → •OH-MAN^-	•OOH + MAN^- → •OOH-MAN^-
C number	G water	G water
C1	−0.76	27.05
C2	−3.27	26.39
C3	−1.71	29.14
C4	−10.86	18.65
C5	−8.48	19.24
C6	−8.60	*b*
C7	−14.79	*a*
C8	−22.32	*a*
C9	2.24	30.12
C10	6.41	19.45
C11	12.04	*a*
C12	6.10	32.77
C14	−23.71	9.14
C15	−18.70	*a*
C17	−11.94	10.30
C18	−11.21	10.25

[a] Products are not formed. •OOH remains dissociated from MAN^-. [b] The hydrogen atom of C6 is removed in order to obtain the deprotonated specie MAN^-.

transfers from carbon sites. On the other hand, such interactions are not present in the TSs corresponding to H transfers from hydroxyl groups. The presence of these stabilizing interactions suggests that the reactivity of the carbon sites might be increased in HMAN. The shortest H···O interaction distance was found for the transition states involved in H transfers from site 18a, for both the neutral and the anionic forms of HMAN. This indicates that the reactivity of this particular site should be increased, with respect to H abstractions from methyl groups of other compounds that do not promote such interactions. At the same time, the absence of these interactions on the TSs corresponding to H transfers from phenolic sites might cause a relative decrease of their reactivity toward •OOH.

The reaction barriers, in terms of Gibss free energies ($\Delta G^{\ddagger}$), are reported in Table 5. For the neutral form of HMAN. It was found that the barriers are systematically higher in aqueous solution than in nonpolar media. Comparing the reactivity of the anion to that of the neutral form (both in aqueous solution), it was found that for H transfers from phenolic sites (3a and 6a) the barrier of channel 3a of the anion is significantly lower than that of channel 6a of neutral HMAN. The difference is about 15 kcal/mol. This difference strongly suggests a higher reactivity of the anionic form. On the contrary, it was also found that for the other HAT paths (13, 15a, and 16), the reactions of the anion have higher barriers than those of the neutral HMAN. The only exception to this trend is channel 16.

The rate constants for the different channels of reaction are reported in Table 6, together with the overall rate coefficient. We have assumed that neither mixing nor crossover between different pathways occurs and therefore the overall rate coefficient, measuring the rate of disappearance of OOH radicals, has been calculated as

$$k_{\text{overall}} = p^{\text{N}} k^{\text{N}}_{\text{tot}} + p^{\text{A}} k^{\text{A}}_{\text{tot}} \quad (4)$$

where p^{N} and p^{A} account for the fractions of the neutral and the anionic forms of mangostin, respectively. The total contributions of each form ($k^{\text{N}}_{\text{tot}}$ and $k^{\text{A}}_{\text{tot}}$) have been estimated by summing up the rate constants of the different reaction channels of the viable mechanisms

$$k^{\text{N}}_{\text{tot}} = k^{\text{N,6a}} + k^{\text{N,13}} + k^{\text{N,15a}} + k^{\text{N,16}} + k^{\text{N,18a}} \quad (5)$$

and

$$k^{\text{A}}_{\text{tot}} = k^{\text{A,3a}} + k^{\text{A,13}} + k^{\text{A,15a}} + k^{\text{A,16}} + k^{\text{A,18a}} \quad (6)$$

According to the overall rate coefficient (Table 6), α-mangostin is predicted to react about 180 times faster in aqueous solution than in nonpolar media. This ratio arises from the increased reactivity of the anion with respect to the neutral form. Comparing the neutral form alone it is more reactive in nonpolar media. According to these results it seems that the efficiency of mangostin as free radical scavenger would be highly influenced by the fraction of the anionic form.

The values of the overall rate coefficients reported in Table 6 indicate that the efficiency of α-mangostin as OOH radical scavenger is similar to that of carotenes ($\sim 10^5$–10^6 M^{-1} s^{-1}),[46] higher than that of allicin ($\sim 8 \times 10^3$ M^{-1} s^{-1}),[47] much higher than that of melatonin ($\sim 2 \times 10^1$ M^{-1} s^{-1})[45] and *N*-acetylcysteine amide (7.58×10^1 M^{-1} s^{-1});[48] and about 15 times lower than that of 2-propenesulfenic acid ($\sim 2.6 \times 10^7$ M^{-1} s^{-1}).[47] It seems worthwhile to call attention on the fact that due to the relative low reactivity of •OOH, compared to other ROS, overall rate coefficients in the order of 10^6 M^{-1} s^{-1} indicate that HMAN/MAN^- is a very good scavenger.

The branching ratios (Table 7) of the different reaction channels, which represent the percent of their contribution to

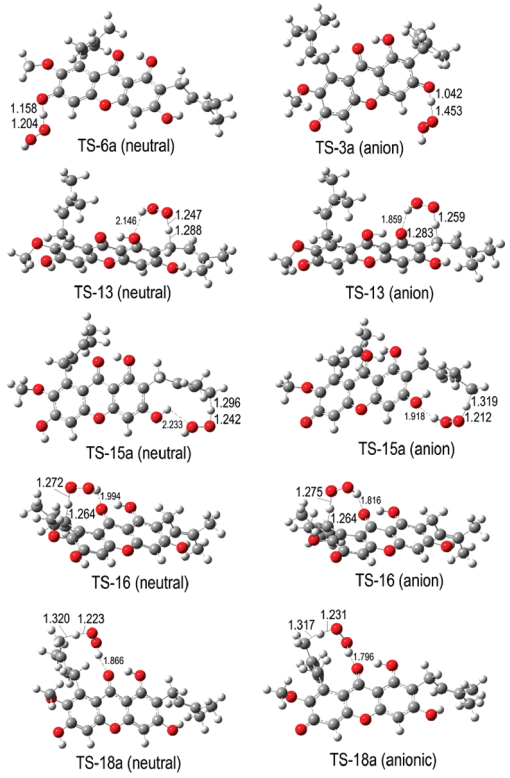


Figure 2. Geometries of the transitions states, fully optimized at M052X/6-31+G(d,p) level of theory.

the total reaction, have been calculated as

$$\Gamma_i = \frac{k_i}{k_{\text{overall}}} \times 100 \qquad (7)$$

where i represents each particular channel.

For the neutral form of HMAN the main channel of reaction was found to corresponds to HAT from site 18a, regardless of the polarity of the environment (Table 7). This can be explained based on the structural characteristics of the TS, which is stabilized by a strong H bonding interaction. For the anionic form (predicted as the active form) the OOH radical scavenging activity of α-mangostin was found to take place almost exclusive from the remaining phenolic site (3a). The contributions of all the other channels of reaction are estimated to be negligible ($\Gamma < 0.01\%$).

3.3. HAT vs SEPT and PCET Mechanisms. As was indicated before in this report, α-mangostin and deprotonated α-mangostin are able to scavenge •OH and •OOH by means of the HAT mechanism. According to this, there are other two mechanisms that should bee considered since they yield the same products as HAT: sequential electron proton transfer (SEPT) and proton coupled electron transfer (PCET). They correspond to single electron transfers followed by, or occurring simultaneously with, proton transfer, respectively. Even though they yield the same products as HAT the influence of the solvent on their feasibility is expected to be different. Although SET and SEPT are likely to be favored by polar environments that promote solvation of the intermediate ionic species, the PCET might be also viable in nonpolar media since the transfer of the proton and the electron occurs simultaneously in this case, and therefore no charged intermediaries are formed.

Table 5. Gibbs Free Energies of Activation ($\Delta G^{\ddagger}$, kcal/mol), at 298.15 K

	HMAN	HMAN	MAN^-
site	benzene	water	water
3a	*a*	*a*	10.67
6a	19.80	25.82	*b*
13	20.98	24.78	25.05
15a	18.32	20.51	23.48
16	18.22	22.44	21.71
18a	15.40	18.83	21.50

[a] Products are not formed. •OOH remains dissociated from MAN^-. [b] The hydrogen atom of C6 is removed in order to obtain the deprotonated specie MAN^-.

Table 6. Rate Constant of the Reaction between HMAN and •OOH (M^{-1} s^{-1}) at 298.15 K

	HMAN	HMAN	MAN^-
site	benzene	water	water
3a	*a*	*a*	2.35×10^6
6a	5.35×10^2	2.07×10^{-2}	*b*
13	5.06×10^{-1}	8.29×10^{-4}	3.02×10^{-4}
15a	4.98×10^1	1.24	1.09×10^{-2}
16	3.13×10^1	2.52×10^{-2}	3.86×10^{-2}
18a	7.19×10^3	2.20×10^1	4.84×10^{-2}
total	7.80×10^3	2.33×10^1	2.35×10^6
overall		1.42×10^6	

[a] Products are not formed. •OOH remains dissociated from MAN^-. [b] The hydrogen atom of C6 is removed in order to obtain the deprotonated specie MAN^-.

Since HAT and PCET mechanisms lead to the same products of reaction, the transition states are usually used to distinct between them. Three different analyses have been performed to that purpose. They are based on atomic spin densities (ASP) on the sites involved in the H transfer, the charge (Q) carried by the H atom that is transferred, and the electronic density of the singly occupied molecular orbital (SOMO). The ASP and Q values, obtained from natural population analysis (NPA) calculations, are reported in Table 8. As the coefficients of the natural orbital carrying the unpaired electron indicate the spin population in all the studied TSs, but TS-3a, of the anion is concentrated on the two atoms which undergo the H exchange, and a small negative value is found on the H atoms that is being transferred. This is consistent with a HAT process.[50] For TS-3a (anion) on the other hand, the spin population is mainly located outside the transfer region. Regarding the charge carried by the H atom that is being transferred, it has been stated that migrating Hs with substantial positive charge are typical of proton migrations.[51,52] For TS-3a (anion) the migrating H was found to have substantial positive charge that is typical of proton migrations.[51,52] For TS-6a (neutral) the charge, on the migrating H, is lower than that for TS-3a (anion) and higher than those found for all the other TSs. In this case the charge criterion is ambiguous since the comparison is not straightforward, i.e., the sites from which the H atoms are being transferred are different in nature (carbon and oxygen).

Table 7. Branching Ratios of the Different Reaction Paths (%) at 298.15 K

	HMAN	HMAN	MAN^-
site	benzene	water	water
3a	*a*	*a*	~100
6a	6.85	0.09	*b*
13	0.01	~0	~0
15a	0.64	5.31	~0
16	0.40	0.11	~0
18a	92.10	94.49	~0

[a] Products are not formed. •OOH remains dissociated from MAN^-. [b] The hydrogen atom of C6 is removed in order to obtain the deprotonated specie MAN^-.

Table 8. Atomic spin densities (ASD) on the atoms involved in the H transfer and charge (Q) carried by the migrating H atom from natural orbital population analyses

	HMAN		MAN^-	
	ASD	Q	ASD	Q
		TS3a		
O6a			0.004	
H			−0.002	0.565
O(OH)			0.001	
		TS6a		
O6a	0.369			
H	−0.097	0.503		
O(OH)	0.525			
		TS13		
C3a	0.554		0.533	
H	−0.130	0.353	−0.133	0.344
O(OH)	0.550		0.571	
		TS15a		
C3a	0.555		0.633	
H	−0.127	0.333	−0.113	0.366
O(OH)	0.560		0.475	
		TS16		
C3a	0.472		0.489	
H	−0.158	0.320	−0.140	0.327
O(OH)	0.673		0.630	
		TS18a		
C3a	0.596		0.577	
H	−0.115	0.363	−0.119	0.356
O(OH)	0.472		0.483	

Even though the PCET mechanism is commonly defined as a concerted electron proton transfer that is not HAT, it has been reported that this is a difficult distinction to make, and that HAT can be considered a particular case of PCET reactions.[53] However, it is commonly accepted that the PCET mechanism can be defined as that in which the proton and the electron are transferred between different sets of orbitals.[51] Therefore the analysis of the singly occupied molecular orbital (SOMO) of the TS seems to be a reliable criterion to differentiate between HAT and PCET processes. The SOMO of HAT transition states is expected to have significant density in atomic orbitals oriented along, or nearly along, the transition vector (donor-H-acceptor). On the contrary, the SOMO of PCET transition states involves p orbitals that are orthogonal to the transition vector.[51] As the plots in Figure 3 show the SOMO in all TSs but TS-6a (neutral) and TS-3a (anion) have a node at the migrating H and are mostly localized on the C···H···O vector, which corresponds to HAT transition states. In contrast, the SOMO of TS-6a (neutral) involves the *p* orbital in the H acceptor (oxygen) perpendicular to the transition vector, indicating that the H and the electron transfers take place from different orbitals, i.e. this TS corresponds to the PCET mechanism. The SOMO of TS-3a (anion) is located far away from the transition vector. We have not found any previous reference about the interpretation of this kind of distribution, but it is certainly not HAT. Taking into account all previously discussed criteria it seems that the H atom in the O6a site of neutral mangostin, and the H atom in the O3a site of anionic mangostin, are transferred to the •OOH radical by PCET, while the H atoms in all the other sites are transferred by HAT.

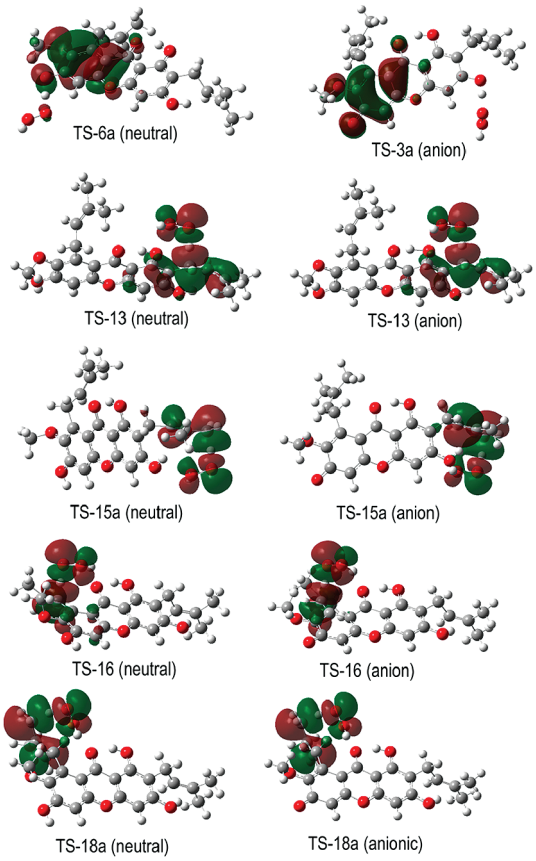


Figure 3. SOMO density surfaces of the HAT/PCET transition states, in aqueous solution, computed with an isodensity value of 0.02 au.

4. CONCLUSIONS

To scavenge •OH and •OOH, the HAT mechanism is thermodynamically and kinetically possible for α-mangostin and its monoanion. Due to the number of reactive hydrogen sites involved in exergoninc processes, it can be stated that for

scavenging •OOH, α-mangostin is not as good as it is for scavenging •OH. For neutral and deprotonated α-mangostin, the RAF mechanism was found to be viable for scavenging •OH but not for •OOH. Due the high reactivity of •OH this is a reasonable result.

According to the overall rate coefficient α-mangostin is predicted to react faster in aqueous solution than in nonpolar media. The efficiency of α-mangostin as free radical scavenger would be highly influenced by the fraction of the anionic form. The effectiveness of α-mangostin as OOH radical scavenger is similar to that of carotenes, higher than that of allicin, melatonin and N-acetylcysteine amide, and lower than that of 2-Propenesulfenic acid. These results indicate that α-mangostin is a very good free radical scavenger.

AUTHOR INFORMATION

Corresponding Author

*E-mail: martina@iim.unam.mx.

ACKNOWLEDGMENT

This study was made possible due to funding from the Consejo Nacional de Ciencia y Tecnología (CONACyT), as well as resources provided by the Instituto de Investigaciones en Materiales IIM, UNAM. The work was carried out, using a KanBalam supercomputer, provided by DGSCA, UNAM and the facilities at Laboratorio de Supercómputo y Visualización en Paralelo of UAM Iztapalapa. The authors would like to acknowledge Caín González, Joaquín Morales, Oralia L. Jiménez, and María Teresa Vázquez for their technical support. A.M. is grateful for financial support from DGAPA-UNAM-México.

REFERENCES

(1) Morton, J. *Fruits of Warm Climates*; Dowling, C. F., Ed.; Creative Resources Systems: Miami, 1987.
(2) Moongkarndi, P.; Kosem, N.; Kaslungka, S.; Luanratana, O.; Pongpan, N.; Neungton, N. *J. Ethnopharmacol.* **2004**, *90*, 161–166.
(3) Pedraza-Chaverrí, J.; Cárdenas-Rodríguez, N.; Orozco-Ibarra, M.; Pérez-Rojas, J. M. *Food Chem. Toxicol.* **2008**, *46*, 3227–3239.
(4) Suksamrarn, S.; Suwannapoch, N.; Phakhodee, W.; Thanuhiranlert, J.; Ratananukul, P.; Chimnoi, N.; Suksamrarn, A. *Chem. Pharm. Bull.* **2003**, *51*, 857–859.
(5) Gopalakrishnan, G.; Banumathi, B.; Suresh, G. *J. Nat. Prod.* **1997**, *60*, 519–524.
(6) Ho, C. K.; Huang, Y. L.; Chen, C. C. *Planta Med.* **2002**, *68*, 975–979.
(7) Williams, P.; Ongsakul, M.; Proudfoot, J.; Croft, K.; Beilin, L. *Free Radical Res.* **1995**, *23*, 175–184.
(8) Mahabusarakam, W.; Proudfoot, J.; Taylor, W.; Croft, K. *Free Radical Res.* **2000**, *33*, 643–659.
(9) Jung, H. A.; Su, B. N.; Keller, W. J.; Mehta, R. G.; Kinghorn, D. *J. Agric. Food Chem.* **2006**, *54*, 2077–2082.
(10) Pedraza-Chaverrí, J.; Reyes-Fermín, L. M.; Nolasco-Amaya, E. G.; Orozco-Ibarra, M.; Medina-Campos, O. N.; González-Cuahutencos, O.; Rivero-Cruz, I.; Mata, R. *Exp. Toxicol. Pathol.* **2009**, *61*, 491–501.
(11) Su, B. N.; Pawlus, A. D.; Jung, H. A.; Keller, W. J.; McLaughlin, J. L.; Kinghorn, A. D. *J. Nat. Prod.* **2005**, *68*, 592–595.
(12) Castañeda-Ovando, A.; Pacheco-Hernández, M. L.; Páez-Hernández, M. E.; Rodríguez, J. A.; Galán-Vidal, C. A. *Food Chem.* **2009**, *113*, 859–871.
(13) Martínez, A. *J. Phys. Chem. B* **2009**, *113*, 4915–4921.
(14) Halliwell, B.; Asechbach, R.; Loliger, J.; Aruoma, O. I. *Food Chem. Toxicol.* **1995**, *33*, 601–617.
(15) Gordon, M. H. *Nat. Prod. Rep.* **1996**, *13*, 265–273.
(16) Schmid, W. *Liebigs Ann. Chem.* **1855**, *93*, 83–88.
(17) Burton, G. W.; Ingold, K. U. *Science* **1984**, *224*, 569–573.
(18) Galano, A. *J. Phys. Chem. B* **2007**, *111*, 12898–12905.
(19) Galano, A.; Vargas, R.; Martínez, A. *Phys. Chem. Chem. Phys.* **2010**, *12*, 193–200.
(20) Martínez, A.; Barbosa, A. *J. Phys. Chem. B* **2008**, *112*, 16945–16951.
(21) Martínez, A.; Vargas, R.; Galano, A. *J. Phys. Chem. B* **2009**, *113*, 12113–12120.
(22) Belcastro, M.; Marino, T.; Russo, N.; Toscano, M. *Theor. Chem. Acc.* **2006**, *115*, 361–369.
(23) Leopolbdini, M.; Russo, N.; Chiodo, S.; Toscano, M. *J. Agric. Food Chem.* **2006**, *54*, 6343–6351.
(24) Leopoldini, M.; Rondinelli, F.; Russo, N.; Toscano, M. *J. Agric. Food Chem.* **2010**, *58*, 8862–8871.
(25) Martínez, A.; Vargas, R.; Galano, A. *Theor. Chem. Acc.* **2010**, *127*, 595–603.
(26) Chiodo, S. G.; Leopoldini, M.; Russo, N.; Toscano, M. *Phys. Chem. Chem. Phys.* **2010**, *12*, 7662–7670.
(27) Leopoldini, M.; Russo, N.; Toscano, M. *Food Chem.* **2011**, *125*, 288–306.
(28) Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994−2011 ACD/Labs)
(29) Frisch, M. J.; et al. *Gaussian 03*, revision E.01; Gaussian, Inc.: Wallingford, CT, 2004.
(30) Cances, M. T.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3037.
(31) Mennucci, B.; Cances, E.; Tomasi, J. *J. Phys. Chem. B* **1997**, *101*, 10506–10517.
(32) Tomasi, J.; Mennucci, B.; Cances, E. *J. Mol. Struct. (Theochem)* **1999**, *464*, 211–226.
(33) Okuno, Y. *Chem.—Eur. J.* **1997**, *3*, 210–218.
(34) - Benson, S. W. *The foundations of chemical kinetics*; Krieger: Malabar, FL, 1982.
(35) Ardura, D.; Lopez, R.; Sordo, T. L. *J. Phys. Chem. B* **2005**, *109*, 23618–23623.
(36) Alvarez-Idaboy, J. R.; Reyes, L.; Cruz, J. *Org. Lett.* **2006**, *8*, 1763–1765.
(37) Alvarez-Idaboy, J. R.; Reyes, L.; Mora-Diez, N. *Org. Biomol. Chem.* **2007**, *5*, 3682–3689.
(38) Mora-Diez, N.; Keller, S.; Alvarez-Idaboy, J. R. *Org. Biomol. Chem* **2009**, *7*, 3682–3690.
(39) Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107–115.
(40) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1935**, *31*, 875–894.
(41) Truhlar, D. G.; Hase, W. L.; Hynes, J. T. *J. Phys. Chem.* **1983**, *87*, 2664–2682.
(42) Eckart, C. *Phys. Rev.* **1930**, *35*, 1303–1309.
(43) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory. Comput.* **2006**, *2*, 364–382.
(44) (a) Velez, E.; Quijano, J.; Notario, R.; Pabón, E.; Murillo, J.; Leal, J.; Zapata, E.; Alarcón, G. *J. Phys. Org. Chem.* **2009**, *22*, 971–977. (b) Vega-Rodríguez, A.; Alvarez-Idaboy, J. R. *Phys. Chem. Chem. Phys.* **2009**, *11*, 7649–7658. (c) Black, G.; Simmie, J. M. *J. Comput. Chem.* **2010**, *31*, 1236–1248. (d) Furuncuoglu, T.; Ugur, I.; Degirmenci, I.; Aviyente, V. *Macromolecules* **2010**, *43*, 1823–1835. (e) Iuga, C.; Alvarez-Idaboy, J. R.; Vivier-Bunge, A. *J. Phys. Chem. A* **2011**, *115*, 5138–5146.
(45) Galano, A. *Phys. Chem. Chem. Phys.* **2011**, *13*, 7147–7157.
(46) Galano, A.; Francisco-Márquez, M. *J. Phys. Chem. B* **2009**, *113*, 11338–11345.
(47) Galano, A.; Francisco-Márquez, M. *J. Phys. Chem. B* **2009**, *113*, 16077–16081.
(48) Galano, A. *Theor. Chem. Acc.* **2011**, *130*, 51−60.
(49) Gao, T.; Andino, J. M.; Alvarez-Idaboy, J. R. *Phys. Chem. Chem. Phys.* **2010**, *12*, 9830–9838.

(50) Olivella, S.; Anglada, J. M.; Soly, A.; Bofill, J. M. *Chem.—Eur. J.* **2004**, *10*, 3404–3410.
(51) Mayer, J. M.; Hrovat, D. A.; Thomas, J. L.; Borden, W. T. *J. Am. Chem. Soc.* **2002**, *124*, 11142–11147.
(52) Turecek, F.; Syrstad, E. A. *J. Am. Chem. Soc.* **2003**, *125*, 3353–3369.
(53) Mayer, J. M. *Annu. Rev. Phys. Chem.* **2004**, *55*, 363–390.