

On the free radical scavenging activities of Ochracene I - A sesquiterpenoid available in marine fungus

Bản về hoạt tính quét gốc tự do của Ochracene I - một hợp chất sesquiterpenoid có trong chiết xuất nấm biển

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Abstract

Ochracene I is a representative sesquiterpenoid compound available in natural marine fungus. Hydroxyl radical scavenging activity of Ochracene I (OCHR) has been studied in aqueous phase using density functional theory M06-2X functional in conjunction with 6-31+G(d,p) basis set. Four common antioxidant mechanisms have been screened: hydrogen transfer (HT), radical adduct formation (RAF), proton loss (PL) and single electron transfer (SET). As a result, OCHR can scavenge OH radical with overall rate constant of $1.88 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ at 298.15K via HT, RAF and SET processes with branching ratio (Γ) being 33.82%, 25.34% and 40.83%, respectively. Furthermore, the SET reaction is the most preponderant one with Γ of 40.83%. Finally, the influence of temperature in range of 290 to 350K on the overall rate constant was also evaluated.

Keywords: marine products, antioxidant, free radical, BDE, PA, IP, kinetics.

Tóm tắt

Ochracene I là một trong những hợp chất sesquiterpenoid điển hình có trong chiết xuất từ nấm biển. Hoạt tính quét gốc tự do hydroxyl của Ochracene I (OCHR) được khảo sát trong dung môi nước bằng cách sử dụng lý thuyết phiếm hàm mật độ (DFT) với phiếm hàm M06-2X kết hợp bộ hàm cơ sở 6-31+G(d,p). Bốn cơ chế chống oxy hóa thông dụng đã được khảo sát gồm, chuyển hydro (HT), cộng gốc tự do vào nối đôi (RAF), mất proton (PL) và chuyển đơn điện tử (SET). Kết quả cho thấy OCHR có thể quét gốc OH với hằng số vận tốc tổng bằng $1.11 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ ở 298.15K thông qua các cơ chế HT, RAF và SET với hệ số phân nhánh (Γ) tương ứng bằng 33.82%, 25.34% và 40.83%. Ngoài ra, phản ứng SET được nhận thấy là phản ứng chiếm ưu thế nhất với hệ số Γ bằng 40.83%. Cuối cùng, ảnh hưởng của nhiệt độ từ 290 đến 350K lên vận tốc phản ứng tổng cũng được khảo sát.

Từ khóa: sản phẩm thiên nhiên biển, chất chống oxy hóa, gốc tự do, BDE, PA, IP, động học.

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1. Introduction

Huge number of natural organic compounds can be found in marine organisms. Among these molecules, terpenoids are considerably abundant and diverse occurring a total percentage of about 60% [1], including monoterpenoids, sesquiterpenoids, diterpenoids, etc. They have also been reported to modulate various biological activities such as anti-inflammatory, antifungal, anticancer, antibacterial, antidiabetic, antiviral as well as antioxidant... [2] Antioxidant properties are also reported for the molecules found in the extract of sponges, algae, and cyanobacteria.

Evaluation of their biological and chemical activities using both computational approaches (virtual screening, density functional theory) and *in-vitro* and *in-vivo* experimental ones have attracted a large range of scientific studies. For example, Dao et al (2020) has shown that a merosquiterpenoids type compound, namely Ochraceopone F, possesses highly potent antioxidant activity *via* radical adduct formation (RAF) mechanism with a rate constant being $3.40 \times 10^0 \text{ M}^{-1} \text{ s}^{-1}$ at the M05-2X/6-311++G(d,p)//M05-2X/6-31+G(d) level of theory in aqueous phase [3].

Thus, the goal of this study is to investigate mechanistic and kinetics evaluation of the OH hydroxyl radical scavenging activity of natural-based Ochracene I in aqueous phase in a wide range of temperature from 290 to 350K. Four common antioxidant processes including hydrogen transfer (HT), radical adduct formation (RAF), proton loss (PL) and single electron transfer (SET) were evaluated via intrinsic thermochemical reactivities (bond dissociation enthalpies – BDE, proton affinities – PA and ionization potential – IP), and reaction kinetic. The obtained results hopefully provide more insight into the free radical scavenging potential of Ochracene I (OCHR).

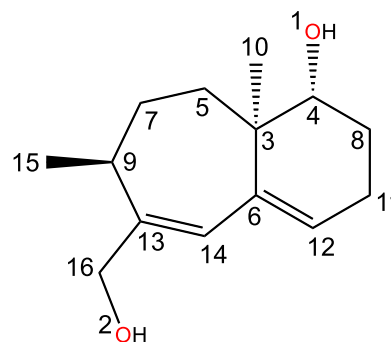


Figure 1.1: Structure of Ochracene I (OCHR)

2. Computational details

Gaussian 16 Rev. A.03 package [4] were used for all geometry optimization and frequency calculations in water at the M06-2X/6-31+G(d,p) level of theory. The M06-2X hybrid functional of Truhlar and Zhao [5] has widely been recommended by several works [6,7], whereas the 6-31G basis set supplemented by diffuse functions (+), one set of d function for heavy atoms, and one set of p function for hydrogen atoms were proved as sufficiently accurate choice for studying thermodynamic and kinetics of molecule – radical reactions [7]. Solvation Model based on the quantum mechanical charge Density of a solute molecule interacting with a continuum [8] was used to reproduce influence of water solvent. Four main mechanisms for hydroxyl (HO•) radical scavenging actions including hydrogen transfer (HT), proton loss (PL), single electron transfer (SET) and radical adduct formation (RAF) were investigated.

In the first approach, intrinsic chemical reactivity parameters including bond dissociation enthalpy (BDE), proton affinity (PA) and ionization potential (IP) were calculated for a rapid screening of the reactivity.

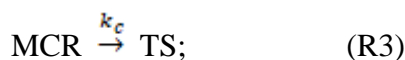
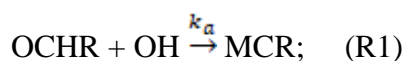
$$\text{BDE (A-H)} = H(\text{A}^\bullet) + H(\text{H}^\bullet) - H(\text{A-H}); \text{ (eq.1)}$$

$$\text{PA (A-H)} = H(\text{A}^-) + H(\text{H}^+) - H(\text{A-H}); \text{ (eq.2)}$$

$$\text{IP (A-H)} = H(\text{AH}^{\bullet+}) + H(\text{e}^-) - H(\text{A-H}); \text{ (eq.3)}$$

Where H denotes the sum of electronic and thermal enthalpies at 298.15 K and 1 atm. The calculated energies of proton (H^+) and electron (e^-) in water were -1046.5 and -13.5 kJ/mol that were calculated based on computational approach suggested previously[9].

Kinetics for HT, RAF and SET reactions between the potential antioxidant Ochracene I (OCHR) and HO^\bullet radical in water were studied by using the pre-reactive complexes scheme proposed by Singleton and Cvetanovic[10]. Briefly, a two-step mechanism was considered:



This scheme involved a fast pre-equilibrium between the reactants and MCR, leading to the hydrogen abstraction/ or radical addition followed by post-reactive complex and products. The effective rate r applied to

reactions (R1-R2) for steady state conditions was defined as follows:

$$r = r_c = k [OH] [OCHR]; \quad (eq.4)$$

Where k was overall rate constant for each pathway and it was calculated by the following equation:

$$k = \frac{k_c k_a}{k_b + k_c} \quad (eq.5)$$

The entropy change in the reverse reaction (R2) was much higher than the reaction (R3). Thus k_b was expected to be larger than k_c , so k can be written as:

$$k = \frac{k_c k_a}{k_b} = k_c K_{a,b} \quad (eq.6)$$

Where $K_{a,b}$ was the equilibrium constant between the isolated reactants and the pre-reactive complex MCR. The equilibrium constant $K_{a,b}$ for the first step can be calculated by basic statistical thermodynamics principles, while k_c was calculated by classical TST formula [11].

$$K_{a,b}(T) = \frac{Q_{MCR}(T)}{Q_{OH}(T)Q_{OCHR}(T)} \exp\left(\frac{E_{OCHR} + E_{OH} - E_{MCR}}{k_B T}\right) \quad (eq.7)$$

$$k_c(T) = \Gamma(T) \times \frac{k_B T}{h} \times \frac{Q_{TS}(T)}{Q_{MCR}(T)} \times \exp\left(-\frac{E_{TS} - E_{MCR}}{k_B T}\right) \quad (eq.8)$$

Where the terms $Q_{OH}(T)$, $Q_{OCHR}(T)$, $Q_{MCR}(T)$, and $Q_{TS}(T)$ were the total partition functions of the reactants OH and Ochracene, the pre-reactive complex MCR, and the TS at the temperature T , respectively. E_{OH} , E_{OCHR} , E_{MCR} , and E_{TS} were the total energies at 0 K (including the zero-point energy corrections) of the reactants OH and Ochracenes, the pre-reactive complex MCR, and the TS, respectively. $\kappa(T)$ was tunneling factor calculated by Eckart method[12], k_B and h were

the Boltzmann and Planck constants, T was the temperature (K). Influence of diffusion rate constant (k_D) on the final values of rate constant was also taken into account in combination with the Smoluchowski equation for steady-state solutions with the Stokes-Einstein equation of which details were described elsewhere[13]. The rate constants were calculated over the temperature range 290–350 K with the GPOP program[14].

3. Results and discussion

3.1. Intrinsic thermochemical properties

The intrinsic reactivity such as BDE, PA and IP allows rapid screening for antioxidant potential of organic molecules *via* formal hydrogen transfer (FHT), proton loss (PL) and single electron transfer (SET) processes, respectively. However, this approach only considers the intrinsic nature of the studied compound itself, but it does not evaluate influence of the chemical nature of interacted free radicals as well as the reactive media. **Table 3.1** resumes BDE and PA values calculated for all the C-H and O-H bonds of OCHR molecule in aqueous phase.

As can be seen in **Table 3.1**, the BDE values of all C-H bonds vary from 341.8 kJ/mol for C16-H to 458.2 kJ/mol for C12-H, whereas the ones of O-H are much higher being 443.0 kJ/mol for O1-H and 443.0 kJ/mol for O2-H. The lowest PA values are found at the O2-H

(219.4 kJ/mol) and O1-H (227.6 kJ/mol) that are much lower than the ones of C-H bonds at which the lowest PA (C-H) is found at the C11-H bond (305.9 kJ/mol). The lowest BDE value of OCHR, 341.8 kJ/mol, is lower than the one of rosmarinic acid (348.5 kJ/mol)[15], and 2-(sec-butyl)-7,8-dimethoxybenzo[de]imidazo[4,5,1-ij][1,6]-naphthyridin-10(9H)-one (355.2 kJ/mol)[16]. Meanwhile, the PA value of OCHR is lower than that of piperidine[3,2-*b*]dimethyl (oxy) aaptamine (251.9 kJ/mol)[16], and pandanusin A (228.4 kJ/mol)[17]. The adiabatic ionization potential (IP) of OCHR is equal to 559.6 kJ/mol while the vertical IP is of 594.3 kJ/mol.

Table 3.1: Bond dissociation enthalpies (BDE), proton affinities (PA) of OCHR calculated in aqueous phase at the M06-2X/6-31+G(d,p) level of theory. All units are in kJ/mol. Adiabatic IP is also calculated and the vertical IP is in parentheses.

Bonds	BDE	PA	IP
			559.6 (594.3)
C4-H	402.7	415.3	
C5-H	411.6	419.3	
C7-H	411.8	415.9	
C8-H	416.9	394.0	
C9-H	345.4	325.8	
C10-H	424.4	402.4	
C11-H	347.4	305.9	
C12-H	458.2	380.9	
C14-H	435.4	357.6	
C15-H	426.3	403.2	
C16-H	341.8	345.4	
O1-H	444.7	227.6	
O2-H	443.0	219.4	

3.2. Mechanistic OH radical scavenging reactions

At first, it is seen that the PA value of ORCH is higher than 219 kJ/mol, thus it is expected that the acidity of C-H and non-aromatic OH group in the side chain (O1-H and

O2-H) are too low and its pK_a value is too high so that the acid-base equilibrium can be considered. Thus, in this work we only investigate the neutral form of OCHR molecule. Reactions between OCHR and OH radical were investigated in aqueous phase to

shed more light into the free radical scavenging process. Firstly, hydrogen transfer (HT) and radical adduct formation (RAF) reactions are considered at the most favorable positions. As shown in **Table 3.1**, C9-H, C11-H and C16-H bonds are represented as the most potential positions for HT process with the lowest BDE

values. Secondly, since the OCHR molecule has only two double bonds including C6=C12 and C13=C14 (**Figure 1.1**), the addition of OH radical to four carbon positions (C6, C12, C13 and C14) is performed. However, the transition state (TS) for the reaction at C6 position cannot be detected although our hard attempts.

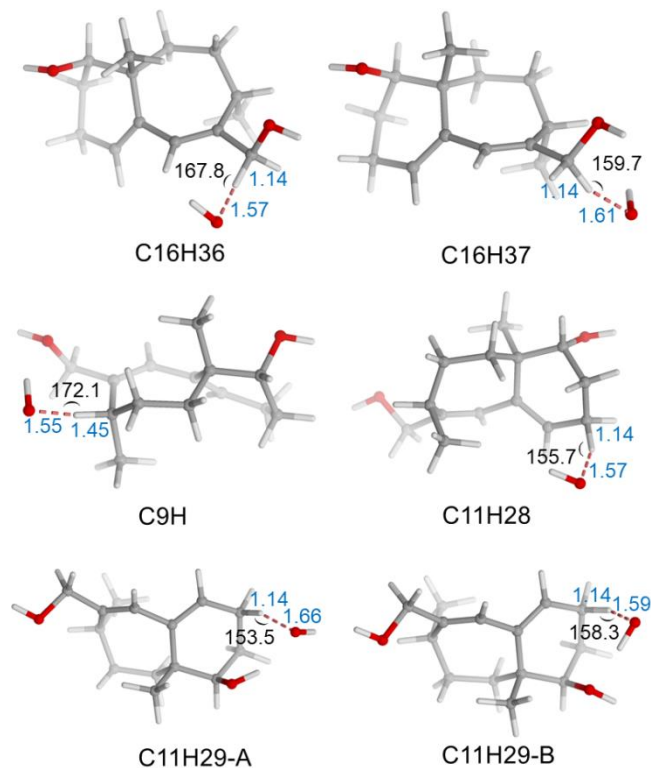


Figure 3.1: Optimized structures of transition states (TSs) for HT reaction between OCHR and OH radical calculated in aqueous phase at the M06-2X/6-31+G(d,p) level of theory. Bond distances are in Å, angles are in degree.

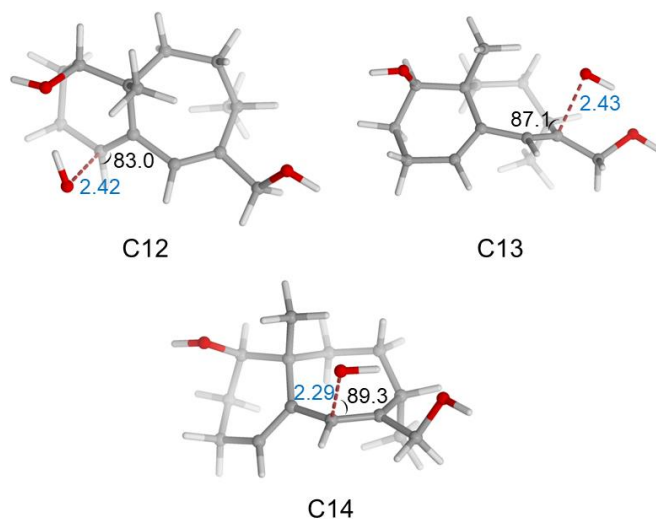


Figure 3.2: Optimized structures of transition states (TSs) for RAF reaction between OCHR and OH radical calculated in aqueous phase at the M06-2X/6-31+G(d,p) level of theory. Bond distances are in Å, angles are in degree.

Figure 3.1 presents transition states (TSs) of six HT reactions at six H atoms located at C16, C9 and C11 positions. It is noteworthy that the geometries of two TSs at C16 are quite different. The lengths of H36-O and H37-O bonds are 1.57 and 1.61 Å, respectively, while the bond angles C16-H36-O and C16-H37-O are 167.8 and 159.7°, respectively. For the TS at C9H, the lengths of C9-H and (C9)H-O bonds are equal to 1.45 and 1.55 Å, respectively. Furthermore, for the TS at C11H, we observe three TS structures, one at H28 atom, and two others at H29 atom that are labeled C11H29-A and C11H29-B. The two TSs structures observed at the C11H29 correspond to two different conformers in which the OH radical forms hydrogen bonds with -O1H

groups in different manners. **Figure 3.2** displays three transition states (TSs) observed for the RAF process of OH radical to C12, C13 and C14 positions of OCHR molecule. The obtained geometries of RAF TSs show that distances C-O(H) are generally varied from 2.29 Å for TS (C14) to 2.43 Å for TS(C13). While the bond angles C-C-O(H) vary from 83.0° for TS(C12) to 89.3° for TS(C14).

3.3. Kinetics of reactions

Figure 3.3 presents potential energy profile at 0K including zero point energy (ZPE) correction for hydrogen transfer (HT) and radical adduct formation (RAF) reactions at the considered positions.

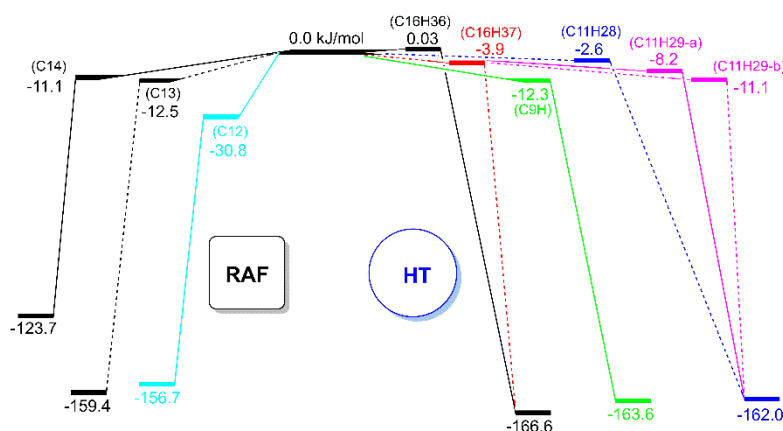


Figure 3.3: ZPE-corrected energy profile (0 K) for hydrogen transfer (HT) and radical adduct formation (RAF) of OCHR and OH radical calculated at the M06-2X/6-31+G(d,p) level of theory in aqueous phase. Enthalpy units are all in kJ/mol.

As can be seen in **Figure 3.3** all the considered reactions are spontaneous and exergonic. Reaction enthalpies of HT reactions are from -166.6 kJ/mol for C16H to -162.0 kJ/mol for C11H, while the ones of RAF reactions are less negative being from -159.4 kJ/mol for C13 to -123.7 kJ/mol for C14 reaction. As expected, most of the reactions with OH radical are barrierless with the relative enthalpies of TS being all negative except the one of C16H36 being 0.03 kJ/mol. As discussed above, the different geometries of TS

(C16H36) and TS (C16H37) tend to difference in energies, *i.e.* 0.03 and -3.9 kJ/mol, respectively. Similarly, three TSs obtained at C11H also have different energies being -11.1, -8.2 and -2.6 kJ/mol for C11H29-b, C11H29-a, and C11H28, respectively. Furthermore, all the TS of RAF reactions have more negative energies than the ones of HT reactions with the relative energies (ΔE) varied from -11.1, -12.5 and -30.8 kJ/mol for C14, C13 and C12 reactions, respectively.

Table 3.2 resumes the TST thermal rate constant, diffusion rate constant, Eckart tunneling factor, diffusion corrected apparent rate constant and branching ratio for all HT, RAF and SET reactions of OCHR and OH radical in aqueous phase at 298.15 K. As expected, the reaction towards OH radical occurs with very fast rate which is in diffusion regime ($k \sim 10^9 \text{ M}^{-1}\text{s}^{-1}$). The thermal rate constant (k_T) at the temperature of 298.15 K varies from 8.62×10^7 to $7.21 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ for HT reactions and from 1.22×10^9 to $2.82 \times 10^{12} \text{ M}^{-1}\text{s}^{-1}$ for RAF reactions, whereas the one for SET reaction is $1.00 \times 10^{11} \text{ M}^{-1}\text{s}^{-1}$. These k_T values are close to diffusion rate constant, k_D , being about $10^9 \text{ M}^{-1}\text{s}^{-1}$. The diffusion-corrected apparent rate constants (k_{app}) vary from 8.39×10^7 to $2.18 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ for HT reactions and from 8.51×10^8 to $2.81 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ for RAF ones. Meanwhile, the k_{app} of SET reaction is $7.67 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$. which is slightly lower than the

value of trolox (i.e. $8.16 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) [18] and the one of tryptamine (i.e. $8.16 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) [19]. Regarding branching ratios (Γ), it is noteworthy that the most preponderant RAF reaction consists in the RAF (C12) occurring 14.96%. The most dominant HT reaction is the HT (C11H29-b) with the branching ratio being 11.61%. In addition, the Γ value of SET reaction is **40.83%**. Generally, the reaction of OCHR with OH radical occurs *via* HT, RAF and SET reactions with the branching ratio of SET being 40.83% that is relatively higher than the ones of HT and RAF being 33.82% and 25.34%, respectively.

Table 3.2: TST thermal rate constant (k_T , $\text{M}^{-1}\text{s}^{-1}$), diffusion rate constant (k_D , $\text{M}^{-1}\text{s}^{-1}$), Eckart factor (κ), diffusion-corrected apparent rate constant (k_{app} , $\text{M}^{-1}\text{s}^{-1}$), and branching ratio (Γ , %) for HT, RAF reactions of OCHR and OH radical calculated at 298.15 K in water.

Rxn.	k_T	k_D	κ	k_{app}	$\Gamma, \%$
HT					
C16H36	8.62×10^7	3.14×10^9	1.00	8.39×10^7	0.45
C16H38	2.12×10^8	3.16×10^9	1.34	1.98×10^8	1.05
C9H	3.13×10^9	3.12×10^9	1.00	1.56×10^9	8.30
C11H28	1.24×10^9	3.16×10^9	1.80	8.92×10^8	4.75
C11H29-a	2.64×10^9	3.17×10^9	1.73	1.44×10^9	7.67
C11H29-b	7.21×10^9	3.13×10^9	2.70	2.18×10^9	11.61
RAF					
C12	2.82×10^{12}	2.82×10^9	1.10	2.81×10^9	14.96
C13	1.22×10^9	2.82×10^9	1.07	8.51×10^8	4.53
C14	1.86×10^9	2.67×10^9	1.05	1.10×10^9	5.83
SET					
	1.00×10^{11}	8.30×10^9	–	7.67×10^9	40.83
Total				1.88×10^{10}	100.00

Finally, **Figure 3.4** displays the influence of temperature in range 290K – 350K on the rate constant values of all the studied reactions between OCHR and OH radical. It is evident that the SET reaction is dominant in the considered temperature range. Then, the RAF(C12), HT(C11H29-b), HT(C11H29-a) and HT(C9H)

reactions are in the following order. As expected, the branching ratios of SET and RAF(C12) reactions having higher k_T values than the diffusion-limit rates both increase strongly from about 40 to 60% and 13 to 20%, respectively, as function temperature, because of the remarkable increase of diffusion rate constant.

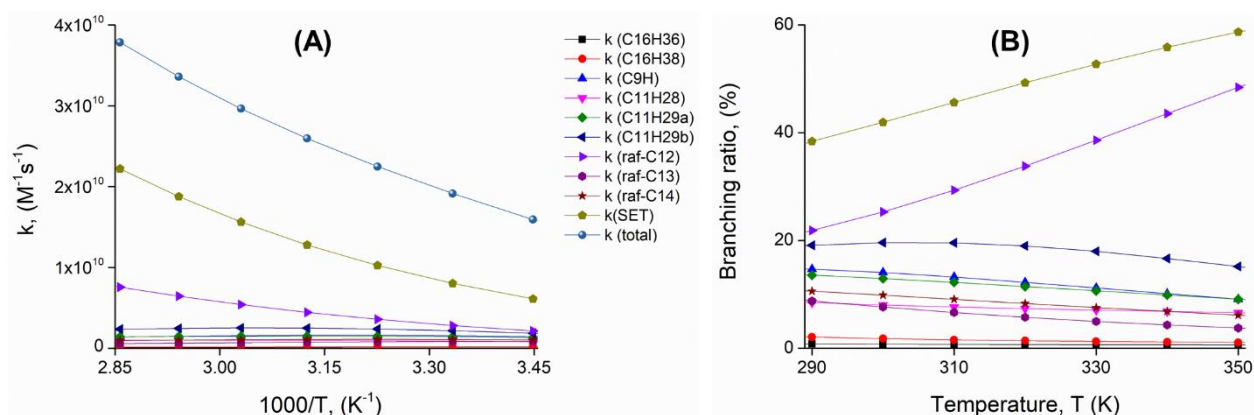


Figure 3.4: (A) Rate constant of HT and RAF reactions for OCHR and OH radical as function of $1000/T$ and (B) Branching ratio as function of temperature from 290 to 350 K.

The overall apparent rate constant for the reaction of OCHR towards OH radical in aqueous phase at 298.15 K is calculated to be $1.88 \times 10^{10} M^{-1}s^{-1}$. This value is comparable with the ones of the OH radical scavenging reaction of others potent antioxidants reported in literature, for example: glutathione ($7.68 \times 10^9 M^{-1}s^{-1}$)[20], caffeine ($2.15 \times 10^9 M^{-1}s^{-1}$)[21], sesamol ($2.37 \times 10^{10} M^{-1}s^{-1}$)[22], melatonin ($1.85 \times 10^{10} M^{-1}s^{-1}$)[23], and trolox ($2.78 \times 10^{10} M^{-1}s^{-1}$)[18]. Based on this comparison, we suggest considering ochracene I as a potential antioxidant *via* the free radical scavenging activity.

4. Conclusions

The mechanistic and kinetic studies of hydroxyl radical scavenging activities of ochracene I, a sesquiterpenoids present in marine fungus, were investigated in aqueous phase at the M06-2X/6-31+G(d,p) level of theory. The obtained results evidently show that OCHR is a very promising antioxidant compound in scavenging OH radical with an overall rate constant being $1.88 \times 10^{10} M^{-1}s^{-1}$ at 298.15K. The hydrogen transfer, radical adduct formation and single electron transfer processes are in competition with the branching ratio being 34.82, 25.34 and 40.83%, respectively. The SET reaction between OCHR and OH radical is the most predominant reaction

occurring up to 40.83%. It is expected that the increase of temperature from 290 to 350K correspondently increases the overall rate constant. Hopefully, the obtained results provide more insight into the potent antioxidant properties of the ochracenes type compounds and so open a wide window for further applications of the compounds.

Acknowledgments

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