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REGULAR ARTICLE

Antioxidant activity of Trolox derivatives toward methylperoxyl radicals: thermodynamic and kinetic theoretical study

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Abstract
The thermodynamic and kinetic aspects of Trolox derivatives reactions with methylperoxyl radical $CH_3OO^{\cdot}$ have been explored through the density functional theory at the M05-2X/631+$G(d,p)$ level of theory. Five reaction mechanisms have been considered in polar and nonpolar media, namely (1) hydrogen atom transfer (HAT), (2) single-electron transfer, (3) sequential proton loss electron transfer, (4) radical adduct formation and (5) sequential proton loss hydrogen atom transfer (SPLHAT). The calculated Gibbs free energies show that HAT is the thermodynamically preferred mechanism in lipid media while SPLHAT is the most favored mechanism in water. The calculated rate constants show that the antioxidant activities of the studied Trolox derivatives against the methylperoxyl radical are 14–260 times faster than that of the reference system (Trolox).

Keywords Trolox derivatives · Antioxidant activity · Thermodynamics · Kinetics · DFT calculations

1 Introduction

Free radicals are produced in living cells by normal metabolism and by exogenous sources such as carcinogenic compounds and ionizing radiations [1]. Oxygen-based free radicals or "reactive oxygen species" (ROS) is a collective term used by biologists to refer to oxygen centered radicals, such as superoxide ($O_2^{\cdot -}$), hydroxyl ($OH^{\cdot}$), alkoxyl ($RO^{\cdot}$) and peroxyl radicals ($ROO^{\cdot}$) [2, 3]. The extensive production of alkoxyl and peroxyl radicals inside the human body can seriously alter the cell structures such as lipids, proteins and DNA, [4] and this phenomenon leads to many severe diseases like cancer, cardiovascular diseases including atherosclerosis and stroke, neurological disorders, renal disorders, liver disorders, hypertension, rheumatoid arthritis, adult respiratory distress syndrome, autoimmune deficiency diseases, inflammation, degenerative disorders associated with aging, diabetes mellitus, diabetic complications, cataracts, obesity, autism, Alzheimer's, Parkinson's and Huntington's diseases [5–14]. Antioxidants are substances that prevent free radical formation in cells and the natural and synthetic phenolic antioxidants containing oxygen and nitrogen heterocyclic aromatic rings are very efficient compounds and they are widely used in several medicinal, pharmaceutical and commercial applications [15–17].

Trolox (H_2TX) is a water soluble α-tocopherol derivative used as a reference against the antioxidant capacity of other compounds (Trolox equivalent antioxidant capacity TEAC). The antioxidant activity of Trolox was investigated in emulsions containing different emulsifiers, and two degradation products were isolated and identified as a quinone and a keto derivative of Trolox [18, 19]. In previous studies [20–22], the antioxidant properties of Trolox against reactive oxygen species (ROS) were investigated and shown to have a good antioxidant protective effect against oxidative stress than most phenolic antioxidants. For this purpose, many derivatives of Trolox have been developed to improve their high efficiency as antioxidant in pharmacy applications and food additives [23]. At physiological media (pH = 7.4), H_2TX is dissociated and both the neutral and anionic forms coexist. So the biological effects of Trolox (pKa = 3.89) are usually ascribed to the mono-anion HTX^- [24]. We note that after the loss of the hydrogen atom from the anion HTX^-, the stable radical $TX^{\cdot -}$ is formed.

Several theoretical studies on the antioxidant activity of Trolox derivatives can be found in the literature. For

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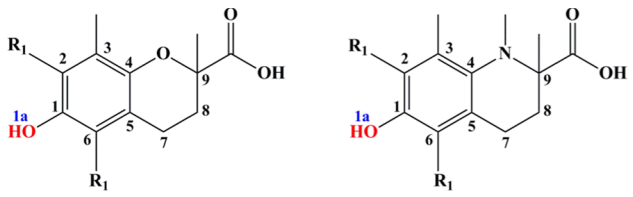
instance, Farmanzadeh et al. [23] studied the different ways for increasing the antioxidant activity of Trolox derivatives and showed that replacing methyl groups with strong electron donating substituents in the *ortho* position leads to a notable decrease of BDE (bond dissociation enthalpy) and consequently the enhancement of the antioxidant activity from a thermodynamic viewpoint. The same authors also showed that Trolox derivatives containing nitrogen heteroatom are better antioxidant than Trolox with the oxygen heteroatom. De Oliveira SÓ et al. [25] applied the virtual screening technique to identify compounds with antioxidant activities similar to Trolox and pointed out to the predominance of the HAT (hydrogen atom transfer) mechanism for these compounds. Alberto et al. [26] studied the free radical scavenging activity of Trolox in aqueous and lipid environments at the SMD-M05-2X/6–31+$G(d,p)$ computational level and several reaction mechanisms and free radicals of different chemical structures were considered. The influence of the pH on molar fractions of the different forms (neutral, mono-anion, di-anion) of Trolox was also studied [26] and the obtained results reveal that Trolox is capable of deactivating a wide variety of free radicals via electron transfer in aqueous solution. However, the efficiency of such activity for each particular radical is influenced by the pH of the environment [26]. Moreover, Trolox was found to be a very good peroxy radical ($ROO^{\cdot}$) scavenger in aqueous solution while its protective effects against this particular kind of free radicals are only moderate in lipid solution when R is a non-halogenated alkyl or alkenyl group [26].

Our aim of the present work is to investigate the antioxidant activity of some designed Trolox derivatives (Scheme 1) against methylperoxyl radical and two ways were used to design new Trolox derivatives H_2TXn ($n=1, 2, 3$): (1) the replacement of the oxygen heteroatom of H_2TX by methylamine (H_2TX2 derivative) and (2) the replacement of the ortho methyl groups of H_2TX and H_2TX2 by strong amino donating groups (H_2TX1 and H_2TX3 derivatives, respectively). In the present study, we have chosen the methylperoxyl radicals $CH_3OO^{\cdot}$ since their half-lives are long enough to ensure that they can be efficiently intercepted by phenolic compounds [27–31].

The reactions between Trolox and methylperoxyl radical $CH_3OO^{\cdot}$ take place through the main possible mechanisms: hydrogen atom transfer (HAT) [32], single-electron transfer (SET) [33], sequential proton loss electron transfer (SPLET) [34], radical adduct formation (RAF) [35] and sequential proton loss hydrogen atom transfer (SPLHAT) [36].



H2TX=Trolox (R1=Me) H2TX2 (R1=Me)

H2TX1 (R1=NH2) H3TX3 (R1=NH2)

Scheme 1 Chemical structures of Trolox derivatives and atom numbering

1.1 HAT mechanism

This mechanism consists of one step in which the proton and the electron are assumed to migrate in the same molecular orbital.

$$H_2TX + CH_3OO^{\cdot} \rightarrow HTX^{\cdot} + CH_3OOH \quad (1a)$$

1.2 SET mechanism

This mechanism is characterized by the ionization of the parent molecule H_2TX, which leads to the formation of a radical cation $HTX^{\cdot+}$.

$$H_2TX^{\cdot} + CH_3OO^{\cdot} \rightarrow H_2TX^{\cdot+} + CH_3OO^{-} \quad (2a)$$

1.3 SPLET mechanism

This mechanism involves two steps. The first step (3a) is the deprotonation of the parent molecule H_2TX under the pH physiologic effect and formation of the stable anion HTX^{-}.

$$H_2TX \rightarrow HTX^{-} + H^{+} \quad (3a)$$

In the second step (3b), the formed anion HTX^{-} transfers an electron to the methylperoxyl $CH_3OO^{\cdot}$ radical which leads to the formation of the radical $HTX^{\cdot}$.

$$HTX^{-} + CH_3OO^{\cdot} \rightarrow HTX^{\cdot} + CH_3OO^{-} \quad (3b)$$

1.4 RAF mechanism

This mechanism corresponds to the addition of the $CH_3OO^{\cdot}$ radical to the carbon–carbon double bond of the aromatic ring leading to the formation of a radical adduct. Under physiological pH, both the neutral and anion species can coexist and consequently two parallel reactions can occur. Reactions (4a–b) correspond to the $CH_3OO^{\cdot}$ addition to the aromatic ring of the neutral and anion species, respectively.

$$H_2TX + CH_3OO^{\cdot} \rightarrow \left[H_2TX - OOCH_3\right]^{\cdot} \quad (4a)$$

$$HTX^- + CH_3OO^{\cdot} \rightarrow \left[HTX - OOCH_3\right]^{-\cdot} \quad (4b)$$

1.5 SPLHAT mechanism

This mechanism takes place in two steps. The first step (5a) is the deprotonation of the parent molecule H_2TX under the pH physiologic effect and formation of the anion HTX^-.

$$H_2TX \rightarrow HTX^- + H^+ \quad (5a)$$

In the second step (5b), the formed anion HTX^- loses an atom to the methylperoxyl $CH_3OO^{\cdot}$ radical and leads to the formation of the anion radical $TX^{-\cdot}$.

$$HTX^- + CH_3OO^{\cdot} \rightarrow TX^{-\cdot} + CH_3OOH \quad (5b)$$

2 Computational methods

All calculations were performed with the Gaussian 09 package [37] and carried out at the M05-2X/6–31+$G(d,p)$ level of theory. Pentylethanoate and water were used as solvents to mimic lipid and aqueous media, respectively. The M05-2X functional has been recommended for kinetic calculations [38–42], also proven its reliability for the calculation of reaction and activation energies relating to radical systems [43]. The SMD implicit model [44] was chosen as a model of solvation for their great ability to use in any solvent or liquid medium for any charged or uncharged solute [45]. For open-shell systems, the unrestricted method was thoroughly applied and the spin contamination of mono-radical species were found slightly greater than 0.75 and they were dropped to the correct value after the annihilation of the spin contamination. The local minima were checked by the true absolute minimums (no imaginary frequencies) and the transition states (TSs) were identified by the presence of one imaginary frequency in the Hessian matrix. The intrinsic coordinate calculations (IRC) were performed in order to connect the TS with the stationary points (reactants and products). The rate constants (k_{TST}) were calculated through the thermodynamic formulation of the conventional transition state theory (TST) [46–48] and corrected by the inclusion of the transmission coefficient $\chi(T)$ using the Wigner formula [49].

$$\chi(T) = 1 + \frac{1}{24}\left[\frac{h\left|\omega^{\neq}\right|}{k_B T}\right]^2 \quad (6)$$

where $\omega^{\neq}$ is the TS imaginary frequency, T is the temperature and k_B is the Boltzmann constant.

Consequently, the final expression for the rate constant (k) becomes:

$$k = \chi(T)\, k_{TST} \quad (7)$$

When rate constants (k) are close to the diffusion-limit, the Collins–Kimball theory is used for the calculation of the apparent rate constants (k_{app}):

$$k_{app} = \frac{k_D\, k}{k_D + k} \quad (8)$$

where k_D stands for the Smoluchowski diffusion rate constant [50].

$$k_D = 4\pi R D_{AB} N_A \quad (9)$$

where N_A, R, D_{AB} are the Avogadro number, the reaction distance and the mutual diffusion coefficient [51–53], respectively

$$D = \frac{k_B T}{6\pi\eta\alpha} \quad (10)$$

where η represents the solvent viscosity ($\eta = 8.91 \times 10^{-4}$ and 8.62×10^{-4} Pa s for water and pentylethanoate, respectively) and α is the solute radius.

For each reaction pathway we have calculated the rate constants together with the total rate coefficients (k_{total}) for each reacting species, and the overall rate coefficients ($k_{overall}$) for the reactions in each solvent. They were calculated for each individual pathway as the sum of the rate constants. To calculate $k_{overall}$, the molar fractions (mf) of the different acid–base species, at the pH of interest (physiological pH = 7.4), were taken into account:

$$k_{overall}^{PE} = k_{total}^{PE} = \sum_{i=1}^{n} k_i^{HX} \quad (11a)$$

$$k_{total}^{W,HX} = \sum_{i=1}^{n} k_i^{HX} \quad (11b)$$

$$k_{total}^{W,X^-} = \sum_{i=1}^{n} k_i^{X^-} \quad (11c)$$

$$k_{overall}^{W,pH=7.4} = mf_{(HX)}^{pH=7.4}\, k_{total}^{W,HX} + mf_{(X^-)}^{pH=7.4}\, k_{total}^{W,X^-} \quad (11d)$$

where HX and X^- represent the neutral and anionic forms of the investigated compounds respectively, PE = Pentylethanoate, and W = Water.

3 Results and discussion

The first pKa values of the Trolox derivatives H_2TXn ($n = 1$–3) have been estimated in this work using Trolox as reference. To that purpose, the proton exchange method [54, 55] was used. It is based on the following reaction scheme:

$$H_2TXn + HTX^- \leftrightarrow HTXn^- + H_2TX \quad (12)$$

where $H_2TXn/HTXn^-$ and H_2TX/HTX^- are the acid/base pairs of Trolox derivatives and Trolo, respectively. The first experimental pKa of Trolox is 3.89 [24]. Within this approach, the pKa values of Trolox derivatives H_2TXn ($n = 1, 2, 3$), in aqueous solution, are estimated using the following expression:

$$pK_a(H_2TXn) = \frac{\Delta G_s}{RT\ln(10)} + pK_a^{exp}(H_2TX) \quad (13)$$

The first pKa values obtained for the studied systems are reported in Table 1, together with the molar fractions of the neutral, and the anionic species, at physiological (pH = 7.4). The first deprotonation involves the carboxylic group. Thus, the mono-anion corresponds to the carboxylate species.

According to the values reported in Table 1, the mono-anion is the dominant form for all Trolox derivatives although a small population of neutral species is expected for H_2TX2 and H_2TX3 derivatives. Consequently, both anionic and neutral species have been included when modeling reactions in aqueous solution.

The thermochemical study of the different mechanisms of reaction has been investigated first since it will determine if a chemical process can actually be observable according to the sign of reaction Gibbs free energies. The ΔG values in pentylethanoate (PE) and in water (W) are calculated for the five mechanisms. For the RAF pathway, all the possible attack sites are considered. The results are recapitulated in Table 2.

Table 2 shows that the ΔG values of the RAF mechanism are considerably positive and higher than those of the HAT mechanism. Consequently, the RAF mechanism is, thermodynamically, disfavored both in lipid and water media

Table 1 First pKa values and molar fraction species, at pH = 7.4 for Trolox derivatives

	pKa	$mf_{neutral}$	mf_{anion}
H_2TX	3.89	≈ 0.000	≈ 1.000
H_2TX1	4.00	≈ 0.000	≈ 1.000
H_2TX2	5.92	0.032	0.968
H_2TX3	5.87	0.029	0.971

Table 2 Gibbs free energies of reaction (ΔG, kcal/mol) for Trolox derivatives

	PE[a]	$W_{neutral}$[b]	W_{anion}[b]	PE[a]	$W_{neutral}$[b]	W_{anion}[b]
	H_2TX			H_2TX1		
SET[c]	61.82	21.50	17.01	51.39	13.78	10.77
HAT OH-1a	−5.73	−8.37	−9.57	−15.01	−18.55	−1.57
RAF						
C1	11.72	9.13	8.63	8.56	6.89	4.77
C2	12.64	10.09	9.86	16.85	13.19	12.90
C3	14.81	10.78	9.83	15.16	11.00	11.21
C4	16.36	12.94	13.05	14.05	12.38	13.38
C5	23.19	19.30	19.91	20.48	16.76	17.86
C6	16.78	14.53	13.23	16.14	14.69	14.53
	H_2TX2			H_2TX3		
SET[c]	48.61	7.77	2.11	44.29	4.99	0.82
HAT OH-1a	−7.84	−15.16	−17.65	−17.21	−20.66	−22.54
RAF						
C1	9.86	6.01	5.24	7.17	4.15	2.90
C2	11.52	7.77	7.47	14.29	9.65	9.51
C3	13.78	9.59	7.71	14.11	11.00	8.52
C4	21.28	17.21	17.73	19.43	16.76	18.77
C5	18.40	16.22	14.33	14.95	14.60	13.04
C6	15.94	11.02	11.41	13.39	10.98	10.59

[a]PE, pentylethanoate (lipid media)

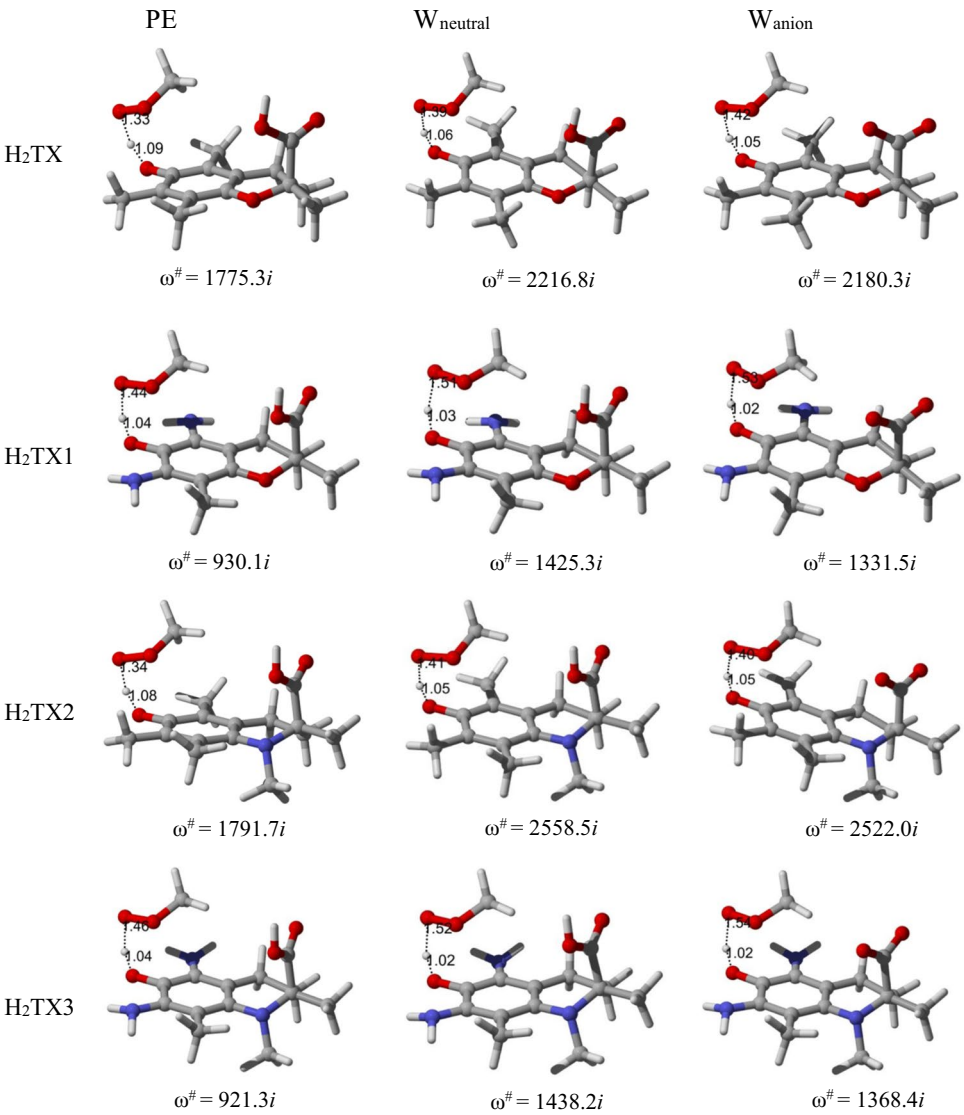
[b]W, water (aqueous solution)

[c]SET from the anion = SPLET

(Table 2). The SET and SPLET mechanisms, corresponding to the neutral species and for anionic species, respectively, are also found to be highly endergonic and consequently disfavored in the both lipid and aqueous media. By contrast, the HAT pathways are found to be remarkably exergonic. Consequently, the abstraction of the hydrogen atom from the OH-1a position is, thermodynamically, favored in all media. We note that the thermochemical viability of the reactions with $CH_3OO^{\cdot}$ is systematically higher for H_2TX3 compared to H_2TX, H_2TX1, H_2TX2 in both lipid and water media. Indeed, site OH-1a of H_2TX3 is characterized by the largest exothermicity for neutral and anionic species (see Table 2). All these findings indicate that H_2TX3 should be a better methylperoxyl radical scavenger than H_2TX1, H_2TX2 and the reference system (Trolox).

The endergonic processes are reversible reactions and consequently their products will not be experimentally obtained. For this reason, the kinetic calculations were performed only for the exergonic reaction pathways. The structures of the located TSs and their corresponding imaginary frequencies are given in Scheme 2. The Cartesian coordinates of the TSs, the reaction barriers and the tunneling corrections used in the calculations of rate constants are provided in the Electronic Supplementary information (ESI). The values of the rate constants (k_{total} and $k_{overall}$) for the studied reactions are given in Table 3.

It was found that H_2TX3 reacts about 260 and 45 times faster than Trolox (H_2TX) in lipid and water solutions, respectively. On the other hand, H_2TX1 reacts about 190 and 44 times faster than H_2TX in lipid and water solutions, respectively. In addition, H_2TX2 reacts about 14.1 and 37.4 times faster than H_2TX in lipid and water solutions, respectively. These results indicate that Trolox derivatives H_2TX1-3 should be much better methylperoxyl radical scavengers than Trolox in lipid and in aqueous solution.



Scheme 2 The optimized structures of the located TSs and imaginary frequencies ($\omega^{\#}$, cm^{-1}), of Trolox derivatives

Table 3 Total and overall rate constants (M^{-1} s^{-1}), for Trolox derivatives

	PE[a]	$W_{neutral}$[b]	W_{anion}[b]	PE[a]	$W_{neutral}$[b]	W_{anion}[b]
	H_2TX			H_2TX1		
HAT OH-1a	3.11×10^{7}	4.44×10^{7}	1.75×10^{8}	5.88×10^{9}	7.71×10^{9}	7.65×10^{9}
Total	3.11×10^{7}	4.44×10^{7}	1.75×10^{8}	5.88×10^{9}	7.71×10^{9}	7.65×10^{9}
Overall	3.11×10^{7}		1.75×10^{8}	5.88×10^{9}	7.65×10^{9}	
Ref. to H_2TX	1		1	1.90×10^{2}	4.40×10^{1}	
	H_2TX2			H_2TX3		
HAT OH-1a	4.38×10^{8}	5.13×10^{9}	6.72×10^{9}	8.14×10^{9}	7.85×10^{9}	7.79×10^{9}
Total	4.38×10^{8}	5.13×10^{9}	6.72×10^{9}	8.14×10^{9}	7.85×10^{9}	7.79×10^{9}
Overall	4.38×10^{8}	6.55×10^{9}	8.14×10^{9}	7.79×10^{9}		
Ref. to H_2TX	1.41×10^{1}	3.74×10^{1}	2.60×10^{2}	4.50×10^{1}		

[a]PE, pentylethanoate (lipid media)

[b]W, water (aqueous solution)

The antioxidant activity of H_2TX1-3 derivative and H_2TX in lipid and aqueous media increases in the flowing order:

H_2TX (Trolox) < H_2TX2 < H_2TX1 < H_2TX3 (in pentylethanoate and water)

Table 3 shows that the reactivity of Trolox derivatives with the methylperoxyl radical increases with the increase of the solvent polarity except for H_2TX3. Indeed, H_2TX1 reacts about 1.30 times faster in water ($\varepsilon=78.35$) than in PE ($\varepsilon=4.72$), while H_2TX2 reacts 14.95 times faster in water than in PE.

Another difference in the reactivity of these compounds is related to the neutral and anionic species. For example, in aqueous solution, the neutral species of H_2TX1 and H_2TX3 react with the same reactivity of the anion species while the H_2TX2 anion reacts about 1.31 times faster than the neutral H_2TX2. Accordingly, it is expected that the pH (i.e., deprotonation) increases the reactivity of Trolox derivatives. In order to analyze the contributions of the different mechanisms and reaction pathways to the overall $CH_3OO^{\cdot}$ scavenging activity of the studied compounds, the corresponding branching ratios (Γ) have been estimated according to:

$$\Gamma_i^{PE} = \frac{k_i}{k_{overall}} \times 100 \tag{12a}$$

$$\Gamma_i^{W,\,pH=7.4} = \frac{mf_i^{pH=7.4}\,k_i}{k_{overall}^{W,\,pH=7.4}} \times 100 \tag{12b}$$

where (i) represents each individual reaction pathway.

The values of the branching ratios are reported in Table 4.

It was found that in lipid media, modeled by nonpolar penthylethanoate solvent that the most important pathway for all Trolox derivatives corresponds to the HAT reaction from site OH-1a (100%). In aqueous solution, at pH = 7.4, the only acid/base species contributing to the overall reactivity of Trolox derivative under such conditions is the mono-anion, while the contribution from the neutral species is about 0–3%. For the H_2TX and H_2TX1 derivatives, the SPLHAT pathway contributes by about 100% to the overall reactivity, while it contributes by about 96.8% and 97.1% for H_2TX2 and H_2TX3, respectively. As we can see from these results, the anion seems to be the key species regarding the methylperoxyl radical scavenging activity for Trolox derivatives. Therefore, the main reaction mechanism can be classified as sequential proton loss hydrogen atom transfer (SPLHAT).

Table 4 The calculated branching ratios (%) for Trolox derivatives

	PE[a]	$W_{neutral}$[b]	W_{anion}[b]	PE[a]	$W_{neutral}$[b]	W_{anion}[b]
	H_2TX			H_2TX1		
HAT OH-1a 100	100	0.0	100	100	0.0	100
	H_2TX2			H_2TX3		
HAT OH-1a 100	100	3.2	96.8	100	2.9	97.1

[a]PE, pentylethanoate (lipid media)

[b]W, water (aqueous solution)

4 Conclusion

The thermodynamic and kinetic aspects of the reactions between Trolox derivatives and methylperoxyl radicals were analyzed using the M05-2X/6–31+$G(d,p)$ method. Different reaction mechanisms (HAT, SET, SPLET, RAF and SPLHAT) were thoroughly investigated. The obtained results pointed out that the largest contributions to the overall methylperoxyl radical scavenging activity are the HAT mechanism in lipid media and the SPLHAT in aqueous solution. The kinetic calculations of the exergonic channels show that the designed derivatives H_2TX1-3 react with $CH_3OO^{\cdot}$ radicals faster than the reference system (Trolox) and the calculated rate constants in pentylethanoate and water increase in the following order:

H_2TX (Trolox) < H_2TX2 < H_2TX1 < H_2TX3.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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