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Novel Trolox derivatives as antioxidants: A DFT investigation

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Abstract: In this paper, the antioxidant activity of 6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox) derivatives were investigated by the density functional theory and the polarization continuum model as a solvent model in order to propose novel derivatives with a higher antioxidant activity from a theoretical viewpoint. The effects of various *ortho* and *meta* substituents on the reaction enthalpies of the antioxidant mechanisms of Trolox derivatives were investigated. In addition, the effect of reducing the number of atoms in the heterocyclic ring and the effect of replacing the oxygen heteroatom of Trolox with other heteroatoms on the antioxidant activity of Trolox derivatives were evaluated. The results showed that NH_2, OH and NHMe substituents in the *meta* and *ortho* positions decreased the homolytic bond dissociation enthalpy (*BDE*) and adiabatic ionization potential (*IP*) values and increased the antioxidant activities of the Trolox derivatives from the theoretical viewpoint. The derivatives **e**, **c** and **d** with NH, S and Se instead of O, respectively, had higher antioxidant activities from the theoretical viewpoint. The obtained results showed that reducing the number of atoms in the heterocyclic ring (derivatives **a** and **b**) decreased the *BDE* and *IP* values and increased the antioxidant activities of the Trolox derivatives from the theoretical viewpoint. The linear dependencies between *BDE* of the O–H bond and *IP* values of the studied Trolox derivatives and the corresponding E_{HOMO} and R(O–H) values could assist in the proposal of novel derivatives with higher antioxidant activity from the theoretical viewpoint.

Keywords: Trolox; antioxidant; free radical; mechanism; bond dissociation enthalpy; adiabatic ionization potential.

INTRODUCTION

Natural and synthetic antioxidants can avoid or at least reduce the peroxidation of lipids by free radicals in the body.[1] Biological antioxidant defense systems eliminated the excess free radicals, however the weakness of the defense systems in body causes oxidative damage to lipids, proteins, and DNA. Among

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the antioxidants, Trolox (6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid) is an important, lipid soluble antioxidant that reduces the oxidative degradation of lipids and proteins.[2] The antioxidant activity of Trolox as a synthesized antioxidant is notable. Trolox (Fig. 1) acts as an effective inhibitor of lipid peroxidation in membrane systems.[3]

Trolox was reported to be an efficient antioxidant in bulk oil but less active in emulsions. Despite a number of different studies, little is known about the mechanisms that affect efficiency in emulsified systems.[4,5] System-related differences were mainly ascribed to the stability and the partitioning of Trolox in emulsions.[6,7] 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.[8,9]

In a previous study, the antioxidant properties of Trolox, a water-soluble analog of tocopherol, against superoxide anion radicals, hydroxyl radicals and hypochlorite were investigated. It scavenged free radicals such as peroxide, hydroperoxide or lipid peroxyl and thus inhibited the oxidative mechanisms that lead to degenerative diseases. Trolox was shown to have an antioxidant protective effect against oxidative stress injury.[10–12]

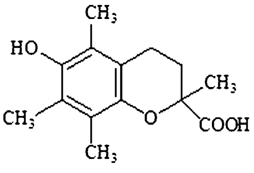
Trolox as a phenolic antioxidant (ArOH) inhibits oxidation *via* two major mechanisms.[13] In the hydrogen atom transfer (HAT) mechanism, the phenolic hydrogen atom is transferred. In the single electron transfer followed by proton transfer (SET–PT) mechanism, a cation radical is formed.[14] The bond dissociation enthalpy (*BDE*) of the phenolic O–H bond is one of the important parameters in evaluating the HAT antioxidant action; the lower is the *BDE*, the easier is the dissociation of the phenolic O–H bond. The ionization potential (*IP*) represents the enthalpy of the first step of the SET–PT process.[15] In the SET–PT mechanism, the ionization potential (*IP*) is the most significant parameter; the lower is the *IP* value, the easier is the electron abstraction.[16]

Although, the *BDE* of the O–H bond and *IP* of Trolox are important parameters in evaluating the antioxidant action; other criteria, including solubility, bioavailability and non-toxicity, must also be considered when designing an effective and safe antioxidant. It was verified that the *BDE* and *IP* represent good theoretical indexes to predict antioxidant activity.[17]

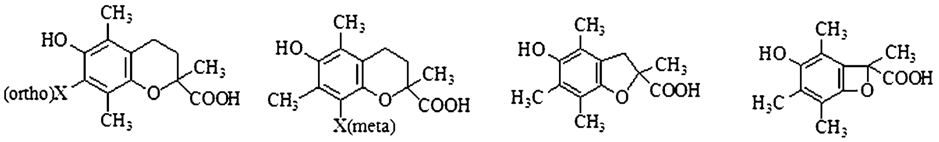
A great deal of effort has been devoted to the design of novel derivatives with higher efficiency in order to develop natural antioxidants.[18] The results of a previous study showed that the antioxidant activity of Trolox mainly comes from its heterocyclic ring, the heteroatom and the substituted methyl groups.[19] The high antioxidant activity of Trolox aroused the present interest to investigate the antioxidant activity of Trolox and 30 novel Trolox derivatives.

In the present study, possible ways of increasing the antioxidant properties of Trolox were investigated using the density functional theory (DFT) in the gas phase and the polarization continuum model (PCM) as the solvent method. Generally, there are three ways to propose novel Trolox derivatives with higher antioxidant activities from the theoretical viewpoint: 1) the replacement of the methyl groups by various *ortho* and *meta* substituents, 2) reducing the number of atoms in the heterocyclic ring and 3) the replacement of the oxygen heteroatom with other atoms.

In this study, the methyl groups on the aromatic ring of Trolox were replaced with various substituents and the effects of these substituents on the antioxidant activity of Trolox were investigated. In addition, the effects of reducing the size of the heterocyclic ring and replacing the oxygen with other heteroatoms on the antioxidant activity of Trolox were considered (Fig. 1).



Trolox



ortho substituted Trolox derivatives

meta substituted Trolox derivatives

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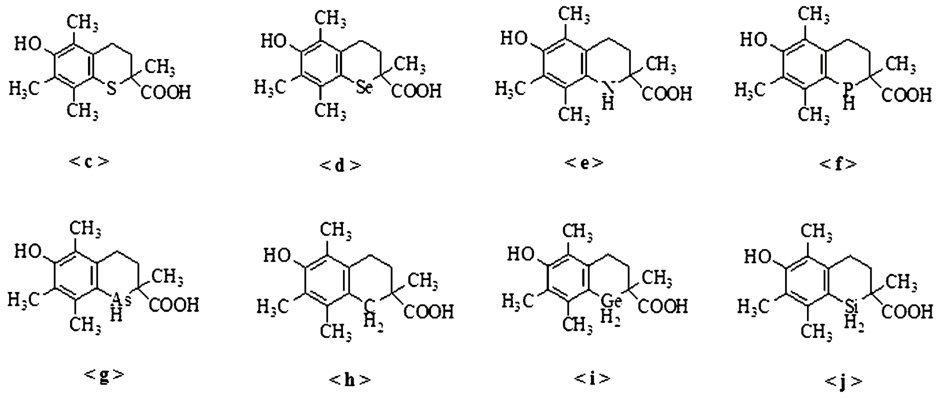

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Fig. 1. Structures of Trolox and Trolox derivatives that were studied in this work (X = NMe_2, NH_2, NHMe, OMe, OH, Et, $CH=CH_2$, Me and *t*-Bu).

The antioxidant activities of novel Trolox derivatives were compared with corresponding values for Trolox. These comparisons could be useful for designing novel Trolox derivatives with higher antioxidant activity from the theoretical viewpoint. Furthermore, in this study, the dependences between the calculated *BDE* of the O–H bonds and the *IP* values with O–H bond lengths and $E_{\rm HOMO}$ values, respectively, were investigated. This could be useful in the selection of suitable candidates to propose as novel Trolox derivatives with enhanced antioxidant activity from the theoretical viewpoint.

COMPUTATIONAL DETAILS

The geometry of studied Trolox derivatives and their respective radicals and cation radicals were optimized using the DFT method with the B3LYP functional and the 6–31G (d, p) basis set.[20,21] Single point calculations were performed by 6–311++G (2d, 2p) basis set.[22,23] The optimized structures were confirmed to be real minima by frequency calculations. All reported enthalpies were zero point values (*ZPE*) corrected with unscaled frequencies. In present paper, water as a polar solvent was chosen and the solvent contributions to the total enthalpies were computed by the polarization continuum model (PCM) as this method presents good accuracy, reliability, adaptability, and a reduced computational effort in describing solvent effects. All calculations were performed using the Gaussian 03 program package.[24] All enthalpies were calculated for 298.15 K and standard pressure.

RESULTS AND DISCUSSION

The BDE *and* IP *values of the substituted Troloxes*

In previous studies, the substituent effects on reaction enthalpies of substituted phenols were investigated in the gas and solvent phase and the results showed that the DFT/B3LYP and PCM methods describe the substituent effect in very good agreement with the corresponding experimental results.[25,26] Also in previous studies, the antioxidant activity of phenolic antioxidants were investigated in the gas and solvent phase.[27–32]

In an earlier study, Ardalan *et al.*[32] calculated the antioxidant activities of Trolox and substituted Trolox derivatives. Their results showed that the *BDE* values of the substituted Troloxes ranged from about 74 to 79 kcal mol^{-1}. Moreover, the results demonstrated that the *BDE* for meta substituted Trolox F, NO_2, CH_3 and C_2H_5 substituents were 3, 5, 4 and 2 kcal* mol^{-1} lower than those for the parent Trolox, in good agreement with previous theoretical studies.[33]

In present study, the *BDE* and *IP* values of substituted Trolox derivatives were theoretically investigated. For complete knowledge of the energetics of the HAT and SET–PT mechanisms, it is important to investigate the effects of substituents on the *BDE* and *IP* values of substituted Trolox derivatives. Replacing the Me groups of Trolox with various substituents could be considered a suitable way to improve the antioxidant activity of Trolox. In this section, the effects of various substituents on the reaction enthalpies of antioxidant mechanisms of

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* 1 kcal = 4184 J

Trolox were investigated in order to find suitable substituents that could decrease the *BDE* and *IP* values and hence, increase the antioxidant activity of Trolox.

The computed *BDE* and Δ*BDE* values for *ortho*- and *meta*-substituted Trolox derivatives (Fig. 1) are reported in Table I. The calculated *BDE* of Trolox reached 381.8 and 370.1 kJ mol^{-1} in the gas phase and water, respectively. For *ortho* NMe$_2$-, NH$_2$- and NHMe-substituted Trolox derivatives, the *BDE* values were lower in comparison to those of Trolox both in gas phase and water.

TABLE I. Calculated *BDE* and Δ*BDE* (kJ mol^{-1}) values of substituted Trolox derivatives

Derivative	Gas				Water			
	Ortho		*Meta*		*Ortho*		*Meta*	
	BDE	Δ*BDE*	*BDE*	Δ*BDE*	*BDE*	Δ*BDE*	*BDE*	Δ*BDE*
Trolox	381.8	0.0	381.8	0.0	370.1	0.0	370.1	0.0
NMe$_2$	347.9	–34.0	360.0	–21.8	344.6	–25.5	355.9	–14.2
NHMe	345.3	–36.6	358.0	–23.8	342.0	–28.1	354.1	–16.0
NH$_2$	343.6	–38.2	358.4	–23.4	340.2	–29.9	352.3	–17.8
OH	354.1	–27.7	361.5	–20.3	349.9	–20.2	357.0	–13.1
OMe	361.6	–20.3	368.9	–12.9	354.5	–15.6	361.6	–8.5
t–Bu	370.2	–11.6	375.1	–6.7	363.3	–6.8	366.0	–4.1
Me	371.7	–10.1	374.6	–7.2	363.8	–6.2	365.2	–4.8
Et	372.1	–9.7	373.6	–8.2	363.8	–6.3	365.5	–4.6
CH=CH$_2$	375.0	–6.9	377.4	–4.4	366.1	–4.0	367.1	–2.9

NMe$_2$, NH$_2$ and NHMe groups in the *meta* position decreased also the *BDE* values for Trolox both in the gas phase and water.

For the *ortho*-OH substituted Trolox, the *BDE* values were lower than those for Trolox, *ca*. 27.7 and 20.2 kJ mol^{-1} in the gas phase and water, respectively. An OH group in the *meta* position decreased the *BDE* values of Trolox in the gas phase and water. For *ortho*-substituted Trolox with alkyl groups, the *BDE* values were 6.9–11.6 and 4.0–6.8 kJ mol^{-1} lower than those for Trolox in the gas phase and water, respectively. The alkyl groups in the *meta* position decreased the *BDE* values of Trolox in gas phase and water.

The computed *IP* and Δ*IP* values for substituted Troloxes in the gas phase and water are reported in Table II. The calculated *IP* values for Trolox reached 689.8 and 432.5 kJ mol^{-1} in the gas phase and water, respectively. The calculated results revealed that lower *IP* values were found for strong electron donating group (EDG) substituents (NMe$_2$, NH$_2$ and NHMe). For the *ortho*-substituted Troloxes with strong EDGs (NMe$_2$, NHMe and NH$_2$), the *IP* values were lower by *ca*. 74.7–77.3 and 53.6–59.0 kJ mol^{-1} in comparison to those of Trolox in the gas phase and water, respectively.

The groups NMe$_2$, NH$_2$, and NHMe in the *meta* position decreased the *IP* value in comparison to that of Trolox in the gas phase and water. The decrease in the *IP* values of Trolox with an OH group were *ca*. 48.1–63.1 and 33.7–44.5 kJ mol^{-1} in gas phase and water, respectively. The *IP* values of Trolox with an alkyl group were lower in comparison to Trolox in the gas phase and water. The decreases in the *BDE* and *IP* values in EDG-substituted Trolox derivatives were the combined result of stabilization of the radicals and radical cations and the destabilization of the parent molecules.

TABLE II. Calculated *IP* and Δ*IP* values (kJ mol^{-1}) of substituted Trolox derivatives

Derivative	Gas				Water			
	Ortho		*Meta*		*Ortho*		*Meta*	
	IP	Δ*IP*	*IP*	Δ*IP*	*IP*	Δ*IP*	*IP*	Δ*IP*
Trolox	689.8	0.0	689.8	0.0	432.5	0.0	432.5	0.0
NMe$_2$	612.5	–77.3	629.7	–60.1	373.5	–59.0	385.4	–47.1
NHMe	614.8	–74.9	628.5	–61.2	375.8	–56.8	384.6	–47.9
NH$_2$	615.1	–74.7	629.6	–60.1	379.0	–53.6	384.2	–48.3
OH	626.7	–63.1	641.6	–48.1	388.1	–44.5	398.9	–33.7
OMe	639.4	–50.4	652.1	–37.7	400.4	–32.1	411.3	–21.3
t–Bu	656.4	–33.3	670.8	–19.0	411.2	–21.4	419.8	–12.7
Me	658.2	–31.5	670.3	–19.5	412.6	–20.0	419.4	–13.1
Et	657.7	–32.0	669.8	–20.0	411.8	–20.8	419.9	–12.7
CH=CH$_2$	663.8	–26.0	672.8	–17.0	415.8	–16.7	423.0	–9.6

In a previous study, theoretical and experimental *BDE* and *IP* values of substituted phenols were collected for the gas phase and water.[34] The results obtained in the present work concerning trends in the effects of substituents on the *BDE* and *IP* values of Trolox derivatives were in agreement with the theoretical and experimental *BDE* and *IP* values obtained for substituted phenols.

Previous studies[27–32] on substituted phenols showed that substituents in the *ortho* or *para* positions exert a stronger influence on the *BDE* and *IP* values when compared with those of the same substituents in the *meta* positions. The computed values of the *BDE* and *IP* values of the substituted Trolox derivatives showed the same trend, namely, substituents in the *ortho* positions exert a stronger influence on the *BDE* and *IP* values than substituents in the *meta* positions. The results showed that Trolox derivatives with lower *BDE* and *IP* values had a higher antioxidant activity in comparison to that of Trolox. Thus, the calculated results showed that replacing the Me group in Trolox with a more electron-donating group, such as NHMe, NH$_2$ and OH, in the *ortho* position could improve the antioxidant activity of Trolox from the theoretical viewpoint.

The BDE *and* IP *values of Trolox derivatives* ***a*** *and* ***b***

Reducing the number of atoms in the heterocyclic ring of Trolox could be considered as a suitable way of improving the antioxidant properties of Trolox. In previous studies, Grisar *et al*. designed a structure analogue based on structure **a**, and also reported that this compound had an inhibition rate 1.8 times higher than that of α-tocopherol on free radicals.[34,35] In this section, the effect of the size of the heterocyclic ring on the reaction enthalpies of the antioxidant mechanisms of Trolox is investigated. The main aim of this section was to identify o novel Trolox derivatives with higher antioxidant activity from the theoretical viewpoint. The novel structures **a** and **b**, obtained by reducing the number of atoms in the heterocyclic ring, are shown in Fig. 1.

The computed *BDE* and *IP* values for the novel derivatives **a** and **b** bin the gas phase and water are reported in Table III. The *BDE* values decreased from those of Trolox for **a** and **b** both in the gas phase and water, respectively; the applies to *IP* values.

TABLE III. Calculated values of *BDE*, Δ*BDE*, *IP* and Δ*IP* (kJ mol^{-1}) for Trolox and Trolox derivatives **a**–**j**

Derivative	Gas		Water		Gas		Water	
	BDE	Δ*BDE*	*BDE*	Δ*BDE*	*IP*	Δ*IP*	*IP*	Δ*IP*
Trolox	381.8	0.0	370.1	0.0	689.8	0.0	432.5	0.0
a	337.8	–44.0	337.1	–33.0	630.1	–59.7	386.3	–46.2
b	344.6	–37.2	340.3	–29.8	640.9	–48.9	393.5	–39.1
c	360.0	–21.8	357.9	–12.1	650.7	–39.1	406.8	–25.7
d	364.8	–17.0	358.4	–11.7	657.2	–32.6	415.0	–17.6
e	333.4	–48.4	332.3	–37.8	622.5	–67.3	378.3	–54.2
f	365.1	–16.7	362.1	–8.0	656.0	–33.8	415.6	–16.9
g	368.8	–13.0	362.5	–7.5	666.9	–22.9	422.9	–9.6
h	393.3	11.5	377.6	7.6	708.7	18.9	441.2	8.7
i	396.0	14.2	379.2	9.1	710.8	21.0	443.7	11.1
j	399.7	17.9	381.2	11.1	714.9	25.2	447.1	14.5

An inspection of the Δ*BDE* values in Table III showed that reducing the number of atoms in the heterocyclic ring from 6 (Trolox) to 5 (structure **a**) and 4 (structure **b**) caused a decrease of *ca*. 37.2–44.4 and 29.8–33.0 kJ mol^{-1} in gas phase and water, respectively. In addition, the *IP* value for Trolox was decreased by *ca*. 48.9–59.7 and 39.1–46.2 kJ mol^{-1} on reducing the number of atoms in the heterocyclic ring from 6 to 5 and 4 in the gas phase and water, respectively.

The p-type orbital of the oxygen atom in the heterocyclic ring of Trolox can delocalize the unpaired electrons thus improving the stability of the phenoxyl radical and phenoxyl cation radical. The computed results indicated that the hydrogen atom and electron donating ability increased with reducing the number of atoms in the heterocyclic ring of Trolox. Therefore, the antioxidant activity of derivatives **a** and **b** are higher than that of Trolox from the theoretical viewpoint.

The BDE *and* IP *values of Trolox derivatives* ***c–j***

In this section, the effects of replacing the oxygen heteroatom with other heteroatoms on the antioxidant activity of Trolox were investigated. Accordingly, the oxygen heteroatom in Trolox was replaced with S, Se, NH, PH, AsH, CH_2,

SiH_2 and GeH_2 groups. The obtained derivatives are shown in Fig. 1 (derivatives **c**–**j**). Determining the effects of each heteroatom on the reaction enthalpies of the antioxidant mechanism could be very important and useful for the proposal of novel antioxidant structures with higher performances.

In previous studies, novel derivatives of vitamin E in which the oxygen heteroatom was replaced with sulfur or selenium heteroatoms were experimentally synthesized and the results (EPR equilibration technique) showed that the *BDE* value of vitamin E could be decreased by *ca*. 4 kJ mol^{-1} by replacing the oxygen heteroatom with a selenium heteroatom.[36,37] In a previous study, the obtained experimental results revealed that derivative **e** has a higher antioxidant potential than Trolox because nitrogen is less electronegative than oxygen and has a high ability to conjugate delocalization of its lone pair of electrons to stabilize a neighboring radical center.[38]

The computed *BDE* and *IP* values of the novel derivatives **c**–**j** are reported in Table III. The results showed that the *BDE* and *IP* values of derivatives **c** and **d** were lower than the corresponding values for Trolox in the gas phase and water. The differences between the *BDE* values of derivatives **c** and **d** with those of Trolox in the gas phase were 21.8 and 17 kJ mol^{-1}, respectively. The results showed that the *BDE* values of derivatives **c** and **d** in water were lower than that of Trolox, 12.1 and 11.7 kJ mol^{-1}, respectively, and that these differences between the *IP* values of derivatives **c** and **d** and corresponding value for Trolox in gas phase were 39.1 and 32.6 kJ mol^{-1}, respectively. Moreover, the *IP* values of derivatives **c** and **d** in water were lower than that for Trolox, *ca*. 25.7 and 17.6 kJ mol^{-1}, respectively. Thus, the antioxidant activity of derivatives **c** and **d** were slightly higher than the activity of Trolox in the gas phase and water from the theoretical viewpoint.

The calculated *BDE* and *IP* values for derivative **e** were lower than the respective values for Trolox in the gas phase and water. The obtained results showed that the differences between the *BDE* values of derivative **e** with those of Trolox were *ca*. 48.4 and 37.8 kJ mol^{-1} in the gas phase and water, respectively. In addition, the results showed that the differences between the *IP* values of derivative **e** and Trolox were *ca*. 67.3 and 54.2 kJ mol^{-1} in the gas phase and water, respectively. This is because nitrogen is less electronegative than oxygen and is able to stabilize comfortably a radical or radical cation form by conjugative delocalization and therefore, derivative **e** has lower *BDE* and *IP* values and higher antioxidant activity in comparison to Trolox in the gas phase and water from the theoretical viewpoint.

The calculated results showed that the *BDE* values of derivatives **f** and **g** were lower than the corresponding value of Trolox by *ca*. 8.0 and 7.5 kJ mol^{-1} in water and *ca*. 16.7 and 13.0 kJ mol^{-1} in gas phase, respectively. In addition, the calculated results showed that the *IP* values of derivatives **f** and **g** were lower than the corresponding value of Trolox by *ca* 33.8 and 22.9 kJ mol^{-1} in the gas phase and by *ca*. 16.9 and 9.6 kJ mol^{-1} in water, respectively.

The computed results showed that the *BDE* and *IP* values for the other studied derivatives (**h**, **i** and **j**) were higher than the corresponding values of Trolox in the gas phase and water from the theoretical viewpoint. A fundamental reason for this could be related to the lack of lone pair of electrons in the case of the CH_2, SiH_2 and GeH_2 groups. Therefore, these groups are not able to stabilize the radical or radical cation formed in the first step of the HAT and SET–PT mechanisms. According to obtained results, replacing the oxygen heteroatom with other heteroatoms, such as NH, S and Se is a suitable way to propose novel Trolox derivatives with higher antioxidant activity than Trolox in gas phase and water from the theoretical viewpoint.

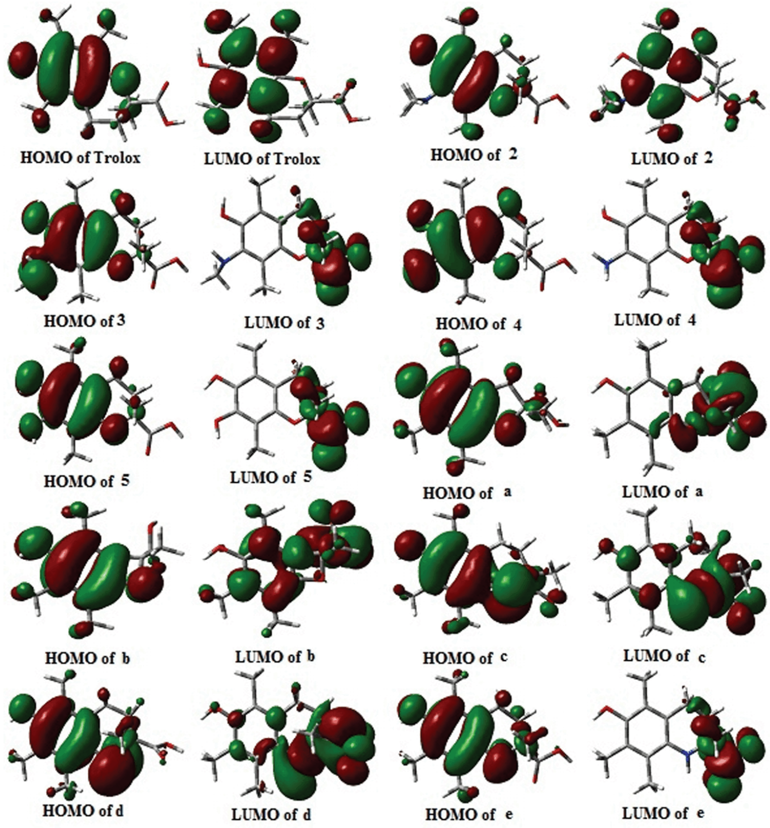
The E_{HOMO} *and* R*(O–H) values of the studied Trolox derivatives*

To accelerate the discovery of novel antioxidants, considerable efforts have been devoted to investigating the structure–activity relationships for antioxidants. The energy of the highest occupied molecular orbital (E_{HOMO}) represents an alternative parameter to assess the electron donating ability of antioxidants. This is widely used in antioxidant studies because of the simple calculation procedure, where the only calculation for parent molecule is required.[39,40] The E_{HOMO} represents an applicable parameter for the prediction of antioxidant activity *via* the SET–PT mechanism.[41] Generally, the higher is the E_{HOMO}, the more active the compound is as an antioxidant.[42]

The computed E_{HOMO} values of the *ortho*- and *meta*-substituted Troloxes and derivatives **a**–**j** are summarized in Table IV. The orbital spatial distribution of the HOMO and LUMO optimized structure of some Trolox derivatives are shown in Fig. 2. The obtained E_{HOMO} value for Trolox was –5.1 eV. The results showed that EWG-substituents increased the absolute E_{HOMO} values and EDG-substituents decreased the absolute E_{HOMO} values in comparison to the corres-

TABLE IV. Calculated E_{HOMO} (eV) and R(O–H) (Å) of the studied Trolox derivatives

Derivative	E_{HOMO}	R(O–H)	Derivative	E_{HOMO}	R(O–H)	Derivative	E_{HOMO}	R(O–H)
Trolox	–5.10	0.96679	Trolox	–5.10	0.96679	**a**	–4.89	0.96927
o-NMe_2	–4.92	0.96655	*m*-NMe_2	–4.92	0.96761	**b**	–4.93	0.96922
o-NHMe	–4.96	0.96659	*m*-NHMe	–4.89	0.96759	**c**	–5.03	0.96928
o-NH_2	–4.98	0.96654	*m*-NH_2	–4.84	0.96756	**d**	–5.05	0.96926
o-OH	–4.99	0.96660	*m*-OH	–4.98	0.96765	**e**	–4.85	0.96915
o-OMe	–5.04	0.96666	*m*-OMe	–5.05	0.96764	**f**	–5.08	0.96945
o-*t*-Bu	–5.03	0.96677	*m*-*t*-Bu	–5.02	0.96770	**g**	–5.10	0.96948
o-Me	–5.04	0.96684	*m*-Me	–5.03	0.96775	**h**	–5.13	0.96952
o-Ethyl	–5.05	0.96682	*m*-Ethyl	–5.06	0.96777	**i**	–5.15	0.96960
o-CH=CH_2	–5.08	0.96679	*m*-CH=CH_2	–5.09	0.96781	**j**	–5.16	0.96965



HOMO of Trolox, LUMO of Trolox, HOMO of 2, LUMO of 2, HOMO of 3, LUMO of 3, HOMO of 4, LUMO of 4, HOMO of 5, LUMO of 5, HOMO of a, LUMO of a, HOMO of b, LUMO of b, HOMO of c, LUMO of c, HOMO of d, LUMO of d, HOMO of e, LUMO of e

Fig. 2. Orbital spatial distribution of HOMO and LUMO optimized structure of Trolox, Trolox derivatives **a**–**e**, and *ortho* NMe_2 (**2**), NH_2 (**3**), NHMe (**4**) and OH (**5**) substituted Trolox derivatives.

ponding value for Trolox. Therefore, Trolox derivatives with strong EDGs, such as NHMe, NH_2 and OH, are better electron donors, *i.e.* they enter the SET–PT mechanism more easily and have lower *IP* values and higher antioxidant activity.

The computed $E_{\rm HOMO}$ values of derivatives **a** and **b** were less negative than that of Trolox. Therefore, derivatives **a** and **b** are better electron donors and have a higher antioxidant activity than Trolox from the theoretical viewpoint. An inspection of the results presented in Table IV revealed that replacing the oxygen heteroatom with S or Se heteroatom caused the $E_{\rm HOMO}$ to become less negative and thus, these derivatives should possess a higher antioxidant activity than Trolox. Replacements of the oxygen heteroatom with the NH heteroatom caused a sharp decrease in the absolute value of $E_{\rm HOMO}$. On the contrary, the other heteroatoms increased the absolute value of $E_{\rm HOMO}$ and caused the corresponding derivatives to have a lower antioxidant activity than Trolox. Therefore, the obtained results showed E_{HOMO} as a suitable antioxidant scale that could enable the antioxidant activity of the studied Trolox derivatives to be predicted.

In a previous study concerning the antioxidant activity of phenolic compounds, it was found that the theoretical method significantly underestimated the vertical of the ionization potentials obtained from E_{HOMO} according to the Koopman theorem.[43] Therefore, it was decided to find the expected linear dependence between the calculated *IP* values and corresponding E_{HOMO} values for studied Trolox derivatives. For the *ortho*- and *meta*-substituted Troloxes and derivatives **a**–**j**, the correlation coefficients reached 0.94, 0.92 and 0.91, respectively. The obtained equations are as follows:

$$IP\ (\mathrm{kJ\ mol^{-1}}) = -435\ E_{\mathrm{HOMO}}\ (\mathrm{eV}) - 1543\ (\textit{ortho}\text{-substituted derivatives})$$

$$IP\ (\mathrm{kJ\ mol^{-1}}) = -227\ E_{\mathrm{HOMO}}\ (\mathrm{eV}) - 479\ (\textit{meta}\text{-substituted derivatives})$$

$$IP\ (\mathrm{kJ\ mol^{-1}}) = -278\ E_{\mathrm{HOMO}}\ (\mathrm{eV}) - 735\ (\text{derivatives } \mathbf{a}\text{–}\mathbf{j})$$

The linearity of dependences could be considered satisfactory and the corresponding equations may be used for a rough estimation of the *IP* values from corresponding E_{HOMO} in the studied Trolox derivatives or *vice versa* (Fig. 2).

The results of a previous study[44] showed that, instead of the properties of the phenolic O–H bond, the *BDE* of *para*- and *meta*-substituted phenols could be successfully correlated with the neighboring C–O bond length or with its shortening after hydrogen atom abstraction. Klein *et al.*[44–46] found good linearity of Δ*BDE vs*. C–N bond length or its shortening after hydrogen atom abstraction for both, *para*- and *meta*-substituted anilines and also for N–H bond length *vs*. *BDE*. These geometric parameters represent suitable descriptors for substituent effects. In a previous study, the results for *meta*-substituted chromanes show that calculated *BDE* values could be successfully correlated with the lengths of the phenolic C–O bond of the studied chromanes.[44–46]

In the present paper, the calculated values of the *R*(O–H) bond lengths corresponding to the studied Trolox derivatives are reported in Table IV. The *R*(O–H) bond length related to Trolox is 0.967 Å. In this study, the dependencies between the *BDE* values of OH bond of *ortho*- and *meta*-substituted Trolox derivatives and derivatives **a**–**j** with corresponding *R*(O–H) values were investigated and the correlation coefficients reached 0.96, 0.93 and 0.94, respectively. The equations obtained from the linear regressions are as follows:

$$BDE\ (\mathrm{kJ\ mol^{-1}}) = 100833R(\mathrm{O–H})\ (\text{Å}) - 97113\ (\textit{ortho}\text{-substituted derivatives})$$

$$BDE\ (\mathrm{kJ\ mol^{-1}}) = 83944R(\mathrm{O–H})\ (\text{Å}) - 80863\ (\textit{meta}\text{-substituted derivatives})$$

$$BDE\ (\mathrm{kJ\ mol^{-1}}) = 120676R(\mathrm{O–H})\ (\text{Å}) - 116614\ (\text{derivatives } \mathbf{a}\text{–}\mathbf{j})$$

The linearity of the dependences could be considered satisfactory and the corresponding equations may be used for rough estimations of the *BDE* values of OH bond from corresponding *R*(O–H) in studied Trolox derivatives or *vice versa*.

These linear dependencies between the *IP* and *BDE* values of the OH bond with the values of E_{HOMO} and *R*(O–H) of the studied Trolox derivatives could be useful in the selection of suitable candidates for the synthesis of novel Trolox derivatives with enhanced antioxidant properties from a theoretical viewpoint.

CONCLUSIONS

In this study, possible ways for increasing the antioxidant activity of Trolox were investigated using the density functional theory in the gas phase and the polarization continuum model in water. The reaction enthalpies related to the individual steps of antioxidant action mechanisms HAT and SET–PT for novel antioxidants based on Trolox were calculated. The calculated results showed that replacing methyl groups with substituents such as NH_2, OH and NHMe in the *ortho* position could improve the antioxidant activity of Trolox from the theoretical viewpoint. The results revealed that derivative **e** with NH heteroatom is a better antioxidant than Trolox from the theoretical viewpoint, due to nitrogen being less electronegative than oxygen, thus being able to comfortably stabilize a radical center by conjugative delocalization and therefore derivative **e** had lower *BDE* and *IP* values in comparison to Trolox. In addition, the results showed that derivatives **c** and **d** with S and Se heteroatoms, respectively, have lower *BDE* and *IP* values in comparison to the corresponding values of Trolox in the gas phase and water. Moreover, the results revealed that reducing the number of atoms in the heterocyclic ring is a suitable way to propose novel Trolox derivatives (**a** and **b**) with lower *BDE* and *IP* values and higher antioxidant activity from the theoretical viewpoint. The theoretical results obtained in present study concerning the antioxidant activity of Trolox derivatives are in agreement with corresponding experimental values previously published. The obtained results show that the *IP* and *BDE* values for the OH bond of novel Trolox derivatives could be successfully predicted from their corresponding E_{HOMO} and *R*(O–H) values respectively. These linear dependencies could be useful for the development of novel derivatives based on Trolox with high antioxidant activity.

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ИЗВОД

НОВИ ДЕРИВАТИ ТРОЛОКСА КАО АНТИОКСИДАНСИ: DFT ИСТРАЖИВАЊЕ

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Истраживано је антиоксидативно дејство деривата тролокса помоћу теорије функционала густине и модела растварача као поларизационог континуума како би се са теоријске тачке гледања могли предложити нови деривати са вишом антиоксидативном активношћу. Истраживани су ефекти различитих *ortho* и *meta* супституената тролокса на

енталпије реакције антиоксидативног механизма. Такође је процењен ефекат смањивања броја атома у хетероцикличном прстену тролокса као и замена кисеониковог атома другим хетероатомом, на антиоксидативну активност. Резултати показују да, са гледишта теорије, NH_2, OH и NHMe супституенти у *meta* и *ortho* положајима смањују вредности енталпије, диспоцијације везе (*BDE*) и јонизационог потенцијала (*IP*), а такође повећавају антикосидативну активност. Деривати **e**, **c** и **d** са NH, S и Se уместо O имају, са гледишта теорије, вишу антиоксидатвну активност. Добијени разултати показују да, са гледишта теорије, смањење броја атома у хетероцикличном прстену (деривати **a** и **b**) смањује *BDE* и *IP* вредности, док повећава антиоксидативну активност. Линеарне зависности између *EDV* вредности O–H везе и *IP* проучаваних деривата тролокса и одговарајућих E_{HOMO} и R(O–H) вредности може бити, са гледишта теорије, од користи за предлагање деривата са вишим антиоксидативним вредностима.

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