

A DFT Study on Antioxidant Activity of Trolox and Substituted Trolox and Their Radicals

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Abstract

Density functional theory (DFT) at B3LYP/6-311G* level was employed to calculate antioxidant activity for Trolox[(+)-6-Hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid] and Substituted Trolox. Bond dissociation energy (BDE), HOMO-LUMO Gap energy, O-H charge differences and O-H bond lengths were calculated. The results are shown that the BDE values of substituted Trolox range from about 74 to 79 kcal/mol, demonstrating that Trolox is an effective chain-breaking antioxidant that prevents lipid peroxidation. Also The small value of gap and the distribution of π -like frontier orbital (HOMO and LUMO) delocalized through the whole molecule (Table 3) corroborate that Trolox and substituted Trolox could be a reactive systems.

Keywords: Trolox; Antioxidant Activity; BDE; Free Radical

1. Introduction

Oxidation causes an irreversible deterioration of biological systems and synthetic polymers. Generally, it corresponds to a free radical chain reaction [1]. The most important reactive radical intermediates formed during oxidation reactions are hydroxyl (HO \cdot), alkoxy (RO \cdot) and peroxy (ROO \cdot) radicals [1-3]. Many experiments indicated that free radicals are necessary to support the life though they are also dangerous to exist in the biological cells and tissues. Under the normal physiological conditions, the free radicals in the body will undergo a process of the producing and scavenging continuously so as to sustain the physiological equilibrium. When the free radicals generated in the body are short and the concentrations are low, the body metabolism may be in disorder and some diseases can be caused [4]. Over the past three decades, the free radical theory has greatly stimulated interest in the role of dietary antioxidants in preventing many human diseases including cancer, atherosclerosis, stroke, rheumatoid arthritis, neurodegeneration, and diabetes [5-9]. A number of epidemiological studies [10, 11] have contributed to build the consensus that diets rich in fruits and vegetables have beneficial effects on human health. The subsequent decrease in the risk of certain pathologies, including cardiovascular diseases and

cancer, is attributed in part to vitamins contained in such food. Those molecules have demonstrated multiple in vitro and in vivo biological properties including antioxidant activities [12].

The main characteristic of an antioxidant is its ability to trap free radicals. Highly reactive free radicals and oxygen species are present in biological systems from a wide variety of sources. These free radicals may oxidize nucleic acids, proteins, lipids or DNA and can initiate degenerative disease. Antioxidant compounds like phenolic acids, polyphenols and flavonoids

Scavenge free radicals such as peroxide, hydroperoxide or lipid peroxy and thus inhibit the oxidative mechanisms that lead to degenerative diseases [13-17]. Trolox, a synthetic and water-soluble analogue of α -tocopherol (Vitamin E), has been shown to have antioxidant protective effect against oxidative stress injury [18-22]. With this proposition, the major objective of this article is to DFT study in antioxidant activity of Trolox and Substituted Trolox for free radical scavenging.

2. Methodology

The Trolox molecule investigated differ mainly in the substituents of C(9) by X=F, NO₂, CH₃ and C₂H₅, (Fig. 1-5).

The precision of DFT which involves the electron

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relation effect is in common better than Hartree–Fock method in which the electron spin is not considered, especially calculating the molecules with hydrogen bonds [23]. Firstly, the original structures of Trolox molecule, Substituted Trolox and the corresponding free radicals (Fig 1-5) were optimized by B3LYP level at 6-311G* basis set [24]. The parameters describing the molecule properties contain: the energies and the disposition of the frontier orbitals HOMO and LUMO, the geometry and the bond disassociation energy (BDE) of hydroxyl groups were calculated. All calculations were carried out with GAUSSIAN 03.

3. Results and discussion

All calculations were performed using Gaussian 03 program package. The geometry of each parent compound and radicals were optimized using DFT method with B3LYP and UB3LYP functional without any constraints. The calculations were performed in 6-311G* basis set.

Bond dissociation energy, BDE, is defined as:

$$\text{BDE} = E(\text{R}^\bullet) + E(\text{H}^\bullet) - E(\text{R-H}) \quad (1)$$

Where $E(\text{R}^\bullet)$ is the total energy of the radical, $E(\text{H}^\bullet)$ is the total energy of the abstracted hydrogen atom, and $E(\text{R-H})$ is the total energy of the molecule [25].

The hydroxyl bond dissociation energies of each corresponding hydroxyl group of radicals were calculated and listed in Table 1 indicated by BDE. In comparison with Trolox whose BDE equals to 74.5925565 and 79.22909125 kcal/mol for 1-OH and 16-OH respectively, it can be seen that the BDE values of substituted Trolox range from about 74 to

79 kcal/mol, demonstrating that Trolox is an effective chain-breaking antioxidant that prevents lipid peroxidation. Moreover, the molecules are observed to have the possibility of generating radicals at positions O(14), O(17) because of the lower values of BDE. Also it can be seen that the BDE for substituted Trolox radicals 16-OH (X=F, CH₃ and C₂H₅) are 3, 2 and 4 kcal/mol lower than those for parent Trolox, in good agreement with previous theoretical studies [26]. But the calculated BDE for substituted Trolox radicals 1-OH (X=F, NO₂, CH₃ and C₂H₅) show that these results are similar to the parent molecule. Therefore electron donor and electron acceptor groups at C1 position does not have any significant effect on the BDE of the O–H bond in comparison to the parent unsubstituted Trolox molecule. From Table 2, we can see the O-H bond lengths for substituted Trolox are longer than those for parent Trolox. It is also interesting to note that the O-H charge differences for parent Trolox are higher than those for substituted Trolox. Also the positive charge on hydrogen atom for substituted Trolox 16-OH (X=F, NO₂, CH₃ and C₂H₅) are higher than the parent Trolox. Thus this Hydrogen can deliver easier than the parent Trolox molecule.

In summary, although the charge difference and bond lengths of O-H plays a role in determining BDE for Trolox and substituted Trolox, BDE are mainly governed by the hydrogen positive charge. Due to the longer bond lengths in substituted Trolox than in Parent Trolox, the BDE for the substituted Trolox 16-OH (X=F, NO₂, CH₃ and C₂H₅) is lower than their parent.

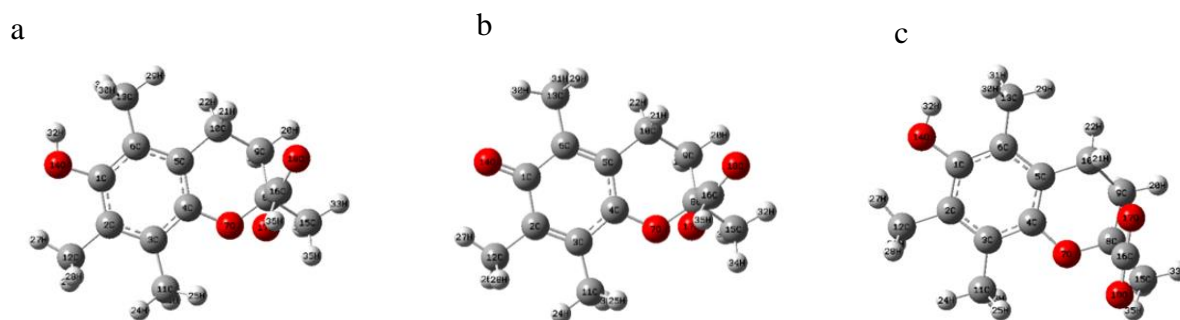


Figure 1. Optimized structure of Trolox (a), 1-OH radical (b) and 16-OH radical (c)

Table 1. Calculated BDE for parent Trolox and corresponding radicals.

Substitution	BDE(kcal/mol)	
	1-OH	16-OH
Parents Trolox	74.5925565	79.22909125
10-F	75.97675875	76.34497575
10-NO ₂	75.376555	75.02471575
10-CH ₃	74.480485	77.66862425
10-C ₂ H ₅	74.915217	75.044733

Table 2. Calculated O-H charge differences and O-H bond lengths for parent Trolox and corresponding radicals.

Substitution	Bond lengths(Ao)		Charge Difference	
	1-OH	16-OH	1-OH	16-OH
Parents Trolox	0.968660	0.968715	0.2031	0.26503
10-F	0.989901	0.991156	0.18843	0.13276
10-NO ₂	0.989834	0.991157	0.18261	0.13742
10-CH ₃	0.989834	0.991157	0.18908	0.13734
10-C ₂ H ₅	0.989834	0.991157	0.19143	0.13501

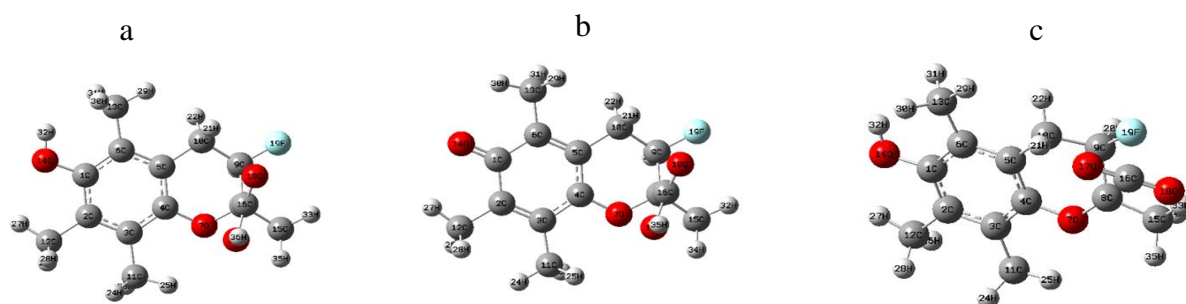
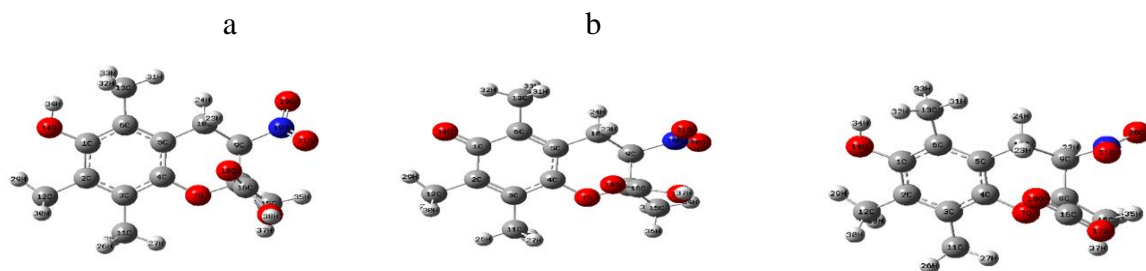
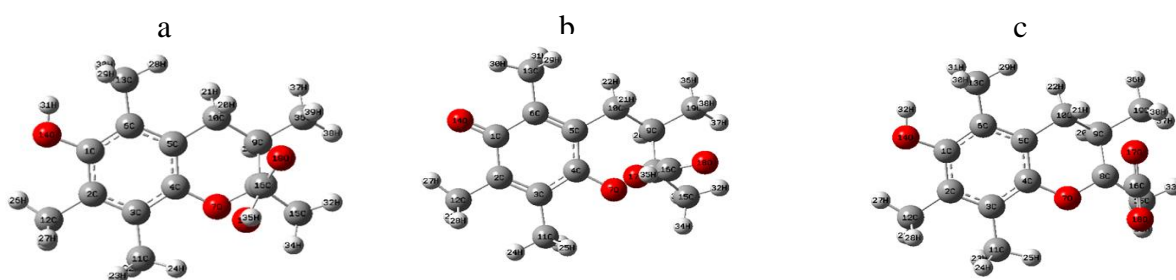
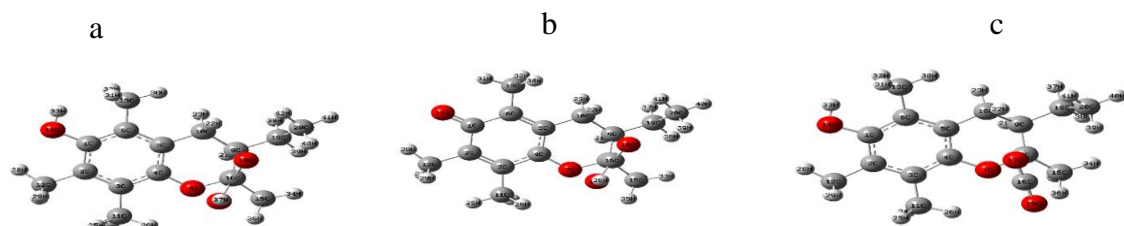


Figure 2. Optimized structure of Substituted Trolox (X=F) (a), 1-OH radical (b) and 16-OH radical (c)

Figure 3. Optimized structure of Substituted Trolox (X=NO₂) (a), 1-OH radical (b) and 16-OH radical (c).Figure 4. Optimized structure of Substituted Trolox (X=CH₃) (a), 1-OH radical (b) and 16-OH radical (c)Figure 5. Optimized structure of Substituted Trolox (X=C₂H₅) (a), 1-OH radical (b) and 16-OH radical (c)

The difference in antioxidant activity between parent Trolox molecule and substituted Trolox, which is reflected in the BDE values calculated above, is often attributed to π -electron delocalization, which leads to the stabilization of the radicals obtained after H-abstraction. This conclusion is drawn assuming that, if π -electron delocalization exists in the parent molecule, it also exists in the corresponding radical. In order to understand the relationship between the electron delocalization and the reactivity of the radicals, one can examine the electron distribution in the singly occupied molecular orbital (SOMO), also called, in this case, the α -highest occupied molecular orbital (α -HOMO). The small value of gap and the distribution of π -like frontier orbital (HOMO and LUMO) delocalized through the whole molecule (Table 3) corroborate that Trolox and substituted Trolox could be a reactive systems [27-29].

Table3. Calculated HOMO, LUMO and HOMO-LUMO Gap energies for parent Trolox and corresponding radicals.

Substitution	HOMO (eV)	LUMO (eV)	HOMO- LUMO Gap(eV)
Parents Trolox	-0.19773	-0.01369	0.18404
Parents Trolox 1-OH	-0.22454	-0.03978	0.18476
Parents Trolox 16-OH	-0.22389	-0.02562	0.19827
10-F	-0.21495	-0.03206	0.18289
10-F, Radical 1-OH	-0.20356	-0.03371	0.16985
10-F,Radical 16-OH	-0.22715	-0.03892	0.18823
10-NO ₂	-0.22233	-0.07655	0.14578
10-NO ₂ , Radical 1-OH	-0.22681	-0.09298	0.13383
10-NO ₂ , Radical 16-OH	-0.23198	-0.08745	0.14453
10- CH ₃	-0.20587	-0.02411	0.18176
10- CH ₃ , Radical 1-OH	-0.21639	-0.03086	0.18553
10- CH ₃ , Radical 16-OH	-0.22373	-0.02582	0.19791
10-C ₂ H ₅	-0.20680	-0.03614	0.17066
10-C ₂ H ₅ , Radical 1-OH	-0.21628	-0.03116	0.18512
10-C ₂ H ₅ , Radical 16-OH	-0.22299	-0.02508	0.19791

From Table 3, we can see the HOMO- LUMO Gap energies for some substituted Trolox are lower than parent Trolox. Thus these substituted Trolox molecules can transfer electron easier than the parent Trolox and can act better as an antioxidant. Generally the antioxidant activity of Trolox and substituted Trolox increase by increasing of O-H bond length, decreasing in BDE and decreasing in HOMO- LUMO Gap energy.

4. Conclusions

O-H bond dissociation energies for Trolox and substituted Trolox have been calculated by using DFT method and 6-311G* basis set. UB3LYP method was

used for the geometry optimization of all the Trolox radicals. Also HOMO-LUMO Gap energy, O-H charge differences and O-H bond lengths were calculated.

The results show that the BDE for substituted Trolox radicals 16-OH (X=F, NO₂, CH₃ and C₂H₅) are 3, 4 and 2 kcal/mol lower than those for parent Trolox, in good agreement with previous theoretical studies. But the calculated BDE for substituted Trolox radicals 1-OH (X=F, NO₂, CH₃ and C₂H₅) show that these results are similar to the parent molecule. Also the small value of gap and the distribution of π -like frontier orbital (HOMO and LUMO) delocalized through the whole molecule

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