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DFT/B3LYP Study to Investigate the Possible Ways for the Synthesize of Antioxidants with High Efficiency Based on Vitamin E

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The possible ways for increasing the antioxidant properties of vitamin E have been investigated with density function theory. The effect of replacing three methyl groups of vitamin E with various substituents such as electron donating and electron withdrawing groups on the antioxidant properties of vitamin E were investigated. Also the effects of the reducing the number of atoms in the heterocyclic ring and replacing the oxygen heteroatom with other heteroatoms on the antioxidant properties of vitamin E were investigated. The novel structures that obtained from replacing methyl groups with substituents such as NH_2, OH, COOH and NHMe have greater antioxidant activity than vitamin E. Obtained results reveal that novel structure that obtained with replacing O with NH hetroatom would be a better antioxidant than vitamin E. The results reveal that reducing the number of atoms in the heterocyclic ring is a better way to synthesize novel antioxidants.

Key Words : Vitamin E, DFT, HOMO, BDE, Antioxidant mechanisms

Introduction

The role of natural antioxidants has lately received much attention because they can avoid or at least significantly reduce the peroxidation of lipids by free radicals, which are related to a variety of disorders and diseases.[1] If excess free radicals are not eliminated by biological antioxidant defense systems, they cause oxidative damage to *in vivo* components such as lipids, proteins, and DNA. Among the antioxidants, vitamin E components represent the most important lipid-soluble peroxyl radical trapping antioxidants, retarding the oxidative degradation of lipids[2] being located in the lipophilic domains of membranes and lipoproteins.[3] The diverse biological activities of natural and synthetic vitamin E derivatives as antioxidants and free radical scavengers are well known. The most biologically active component of vitamin E, namely α-tocopherol (α-TOH, Fig. 1(a)) acts as an effective inhibitor of lipid peroxidation in membrane systems.[4] The phenolic antioxidants (ArOH) inhibit oxidation by transferring their phenolic H atom to chain-carrying peroxyl radical ($ROO^{\bullet}$) at a rate much faster than that of chain propagation.[5] This yields a nonradical product (ROOH) that cannot propagate the chain reaction

$$ROO^{\bullet} + ArOH \rightarrow ROOH + ArO^{\bullet} \quad (1)$$

It is proposed[6,7] that chain-breaking antioxidants can play their protective role via two major mechanisms. In the first one, H-atom transfer (HAT) mechanism, the phenolic H atom is transferred in one step, as shown in Eq. (1). In the HAT mechanism, the bond dissociation enthalpy (BDE) of the phenolic O-H bond is one of the important parameters in evaluating the antioxidant action; the lower the BDE, the easier the dissociation of the phenolic O-H bond. The second mechanism, single electron transfer followed by proton transfer (SET-PT), takes place in two steps

$$ROO^{\bullet} + ArOH \rightarrow ROO^{-} + ArOH^{+\bullet} \quad (2.1)$$

$$ArOH^{+\bullet} \rightarrow ArO^{\bullet} + H^{+} \quad (2.2)$$

In the first step, cation radical is formed (Eq. 2.1). In the second one, deprotonation of $ArOH^{+\bullet}$ occurs (Eq. 2.2), followed by the protonation of ROO^{-}.

$$ROO^{-} + H^{+} \rightarrow ROOH \quad (2.3)$$

Ionization potential (IP) and proton dissociation enthalpy (PDE)[8,9] represent enthalpies of the SET-PT process. In the SET-PT mechanism, the ionization potential (IP) is the most significant parameter; the lower the IP value, the easier the electron abstraction. However, low IP values are favorable to raise the electron-transfer reactivity, they enhance the chance of generating a superoxide anion radical through the transfer of the electron directly to surrounding O_2.[10,11] Recently, another mechanism has been discovered.[12-15] This was named sequential proton loss electron transfer (SPLET), taking place in two steps (Eqs. 3.1 and 3.2)

$$ArOH \rightarrow ArO^{-} + H^{+} \quad (3.1)$$

$$ArO^{-} + ROO^{\bullet} \rightarrow ArO^{\bullet} + ROO^{-} \quad (3.2)$$

$$ROO^{-} + H^{+} \rightarrow ROOH \quad (3.3)$$

The reaction enthalpy of the first step (Eq. 3.1) corresponds to the proton affinity, PA, of the phenoxide anion

Abbreviations: Density Functional Theory (DFT), Bond Dissociation Enthalpy (BDE), Ionization Potential (IP), Proton Affinity (PA), Single Electron Transfer followed by Proton Transfer (SET-PT), Sequential Proton Loss Electron Transfer (SPLET), Hydrogen Atom Transfer (HAT), HOMO (Highest Occupied Molecular Orbital).

(ArO^-).[16-18] In the second step (Eq. 3.2), electron transfer from phenoxide anion to $ROO^\bullet$ occurs and the phenoxy radical is formed. The reaction enthalpy of this step is denoted as oxidation/reduction enthalpy, O/RE. From the antioxidant action viewpoint, the net result of SPLET is the same as in the two previously mentioned mechanisms, the transfer of hydrogen atom to the free radicals. The biological implications and the great potential of vitamin E as antioxidant aroused our interest in elucidating its antioxidant activity by means of DFT/B3LYP calculations, which have been successfully used for a variety of antioxidants.[19,20] In many experimental and theoretical studies[21-27] the tail of tocopherols is replaced by hydrogen, methyl or ethyl group because the phytyl chain has little effect on the BDE, IP, PA of α-tocopherol. Therefore, in this study, we have also used a model structure, 3,4-dihydro-5,7,8-trimethyl-2*H*-chroman-6-ol molecule (Fig. 1(b)). As compared with phenolic antioxidant, the antioxidant activities of vitamin E mainly come from its heterocyclic ring, the heteroatom and the substituted methyl groups. The great deals of effort have been devoted to design and synthesize the derivatives with novel structures and properties in order to development of natural antioxidant as potential antioxidant activity. In order to develop novel antioxidants better than vitamin E, several efforts have been made to synthesize vitamin E analogues.[28-37] In this article, the possible ways for increase the antioxidant properties of vitamin E have been investigated with density function theory. Generally, there are three ways to develop novel antioxidants better than vitamin E: (1) the replacement of methyl groups by electron donating and electron withdrawing groups, (2) the replacement of oxygen heteroatom with other atoms and (3) reducing the number of atoms in the heterocyclic ring.

In previous studies[32-34] we investigated the effect of replacing three methyl groups by electron donating and electron withdrawing groups on the antioxidant properties of vitamin E in gas phase. In this paper, the effects of the reducing the size of heterocyclic ring and the replacing O with other heteroatoms on the antioxidant properties of vitamin E were investigated by density functional method, which has been testified to be a useful and economical method to investigate antioxidant mechanism of molecules.[38-40] In this paper, three methyl groups on aromatic ring of α-TOH were replaced with hydrogen atom, and the resulted molecule represents a basic structure of vitamin E (Figure 1(c)). The reaction enthalpies of new structures were compared with corresponding value of basic structure of the vitamin E. This comparison can be useful for designing new structures with high antioxidant properties.

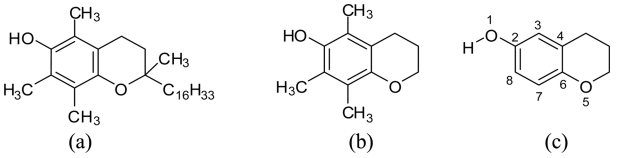


Figure 1. (a) Structure of α-tocopherol. (b) 3,4-dihydro-5,7,8-trimethyl-2*H*-chroman-6-ol. (c) The basic structure of vitamin E (3,4-dihydro-2*H*-chroman-6-ol).

Computational Details

The geometries of the molecules and respective radicals, radical cations and anions were optimized using DFT method with B3LYP functional[41-43] and the 6–311++G (2d,2p) basis set[41,42] in the gas-phase. The ground-state geometries of molecules were optimized at restricted B3LYP level and the geometry of the radicals, radical cations, anions were optimized at the unrestricted B3LYP open shell (half electron) level. The optimized structures were confirmed to be real minima by frequency calculation. For the species having more conformers, all conformers were investigated. The conformer with the lowest electronic energy was used in this work. All reported enthalpies were zero-point (ZPE) corrected with un-scaled frequencies. All calculations were performed using *Gaussian 98* program package.[44] All enthalpies were calculated for 298.15 K and 1.0 atmosphere pressure.

Results and Discussion

Total enthalpies of the studied species X, H(X), at the temperature T are usually estimated from the expression (4)[8,45]

$$H(X) = E_0 + ZPE + \Delta H_{trans} + \Delta H_{rot} + \Delta H_{vib} + RT \quad (4)$$

where E_0 is the calculated total electronic energy, ZPE stands for zero-point energy, ΔH_{trans}, ΔH_{rot}, and ΔH_{vib} are the translational, rotational, and vibrational contributions to the enthalpy, respectively. Finally, RT represents PV-work term and is added to convert the energy to enthalpy. From the calculated total enthalpies we have determined following quantities:

$$BDE = H(ArO^\bullet) + H(H^\bullet) - H(ArOH) \quad (5)$$

$$IP = H(ArOH^{+\bullet}) + H(e^-) - H(ArOH) \quad (6)$$

$$PDE = H(ArO^\bullet) + H(H^+) - H(ArOH^{+\bullet}) \quad (7)$$

$$PA = H(ArO^-) + H(H^+) - H(ArOH) \quad (8)$$

$$O/RE = H(ArO^\bullet) + H(e^-) - H(ArO^-) \quad (9)$$

The calculated gas-phase enthalpy of proton, $H(H^+)$, and electron, $H(e^-)$, is 6.197 and 3.145 kJ mol^{-1}, respectively.[46]

Effect of Replacing the Three Methyl Groups with Various Substituents on Reaction Enthalpies. The replacing the three methyl group of vitamin E with various substituents can be considering as a suitable way to improve the antioxidant properties of vitamin E. The substituents such as NH_2, NHMe, OH and COOH can form hydrogen bonding. Novel structures with these substituents have more active than vitamin E in reaction with free radicals. The substituent such as $NHMe_2$, *t*-Bu, Ethyl and NHMe have more electron donating than Me group therefore these substituent can stable than Me group vitamin E ($ArOH^{+\bullet}$) and reduce the IP value. The substituent such as CN, NO_2 and CF_3 have more electron withdrawing than Me group therefore these substituent can stable anion form of vitamin E rather than Me group and reduced the PA value. Each substituent that reduce the value of reaction enthalpies of the first step of three

mechanisms (BDE, IP and PA) can replace with Methyl group in vitamin E. Therefore better antioxidant structures rather than vitamin E must be have low BDE, IP and PA values. In this paper, the calculated BDE, IP and PA value for the basic structure of vitamin E in gas-phase reached 309.5, 676.7 and 1499.4 kJ mol^{-1}. In previous studies[32-34] three methyl groups of vitamin E were replaced with various substituents such as electron donating and electron withdrawing groups. The effect of these replacements on the reaction enthalpies of first step of antioxidant mechanism of vitamin E was investigated. The obtained results show that electron donating substituents lead to a decrease in BDE and IP values in comparison to those of basic structure. The lowest BDE and IP values for *ortho* and *meta* substituents were found in the case of structures with highest electron donating groups such as NMe_2, NH_2, NHMe and OH. The computed results reveal that substituents in *ortho* position have more effect on reaction enthalpies in comparison to *meta* position. For structures with highest electron donating group, the BDE and IP values can be decreased *ca.* 30-45 and 45-70 kJ mol^{-1} lower than those of basic structure of vitamin E, respectively. These results stem from the fact that the radical or radical cation derived from the hydrogen or electron abstraction of any of structures can be stabilized by the electron-donating power of the *ortho* hydroxyl and the intermolecular hydrogen bond formed. Alternatively, if the substituent can act as a hydrogen bond donor to the phenolic oxygen atom, the corresponding phenoxyl radical may be stabilize than basic structure, therefore the BDE and IP values of these structures can be lower than those of vitamin E. Also, the obtained results show that electron withdrawing substituents caused the PA values decreased in comparison to basic structure of vitamin E. The lowest PA values for *ortho* and *meta* substituent were found in the case of highest electron withdrawing group such as NO_2, CF_3 and CN. For the structures with highest electron withdrawing group, the PA values can be decreased *ca.* 40-65 kJ mol^{-1} lower than those of vitamin E. Therefore, the replacement of three methyl groups with the highest electron donating and electron withdrawing substituents in new structures results in the increase of antioxidant properties.

Effect of Reducing the Number of Atoms in the Heterocyclic Ring on Reaction Enthalpies. Reducing the number of atoms in the hetrocyclic ring can be considering as the second way to improve the antioxidant properties of vitamin E. In this section, the effect of reducing the number of atoms in the heterocyclic ring on the reaction enthalpies corresponding to the antioxidant mechanisms of vitamin E were investigated. Figure 2 shows new structures obtained from reducing the number of atoms in the heterocyclic ring. In this paper, the structure **1a** represents the basic structure of vitamin E.

The computed BDE, IP and PA values for these new structures are reported in Table 1. Relative BDE, IP and PA values, the difference between BDE, IP and PA values of novel structures (**1b**, **1c** and **1d**) and basic structures (**1a**), are also summarized in the Table 1. The BDE, IP and PA

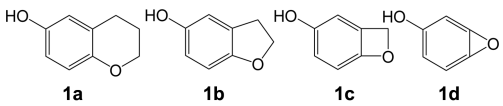


Figure 2. Studied structures with reducing the number of atoms in the heterocyclic ring.

values of **1a**, **1b**, **1c**, and **1d** were calculated to investigate the effect of heterocyclic ring with different number of atoms on antioxidant properties of vitamin E. The BDE value decrease from 309.5 to 280.8 kJ mol^{-1} for the structures **1a** and **1d**, respectively; while the IP value increases from 676.7 to 723.8 kJ mol^{-1}. An inspection of the ΔBDE values appearing in Table 1 shows that reducing the number of atoms in the heterocyclic ring from 6 to 5, 4 and 3 causes a decrease *ca.* 11.3, 15.4 and 28.7 kJ mol^{-1}, respectively. Also, the IP value of basic structure increases *ca.* 8.9, 35.2 and 47.0 kJ mol^{-1} by reducing the number of atoms in the heterocyclic ring from 6 to 5, 4 and 3, respectively. Computed results indicated that the hydrogen atom donating ability to increase while the electron donating groups ability to decrease with reducing the number of atoms in the heterocyclic ring. The PA value decrease from 1499.4 to 1461.2 kJ mol^{-1} for the structures **1a** and **1d**, respectively. An inspection of the ΔPA values shows that reducing the number of atoms in the heterocyclic ring from 6 to 5, 4 and 3 causes a decrease ca 2.7, 8.3 and 38.1 kJ mol^{-1}, respectively. Therefore, the proton donating ability increases with reducing the number of atoms in the heterocyclic ring. According to obtained results, reducing the number of atoms in the heterocyclic ring is a suitable way to synthesize novel antioxidant better than vitamin E. The π-type orbital of oxygen atom in the heterocyclic ring of vitamin E can delocalize the unpaired electrons improving the stability of the phenoxyl radical. In this paper, the spin density of **1a**, **1b**, **1c**, and **1d** radical structures were calculated. The computed spin density of the **1a**, **1b** and **1c** radical structures mainly distributes on the C3, C6, and C8 of benzene ring and O1. Calculated spin density of C6 are 0.051, 0.229, 0.243 and 0.267 for **1d**, **1c**, **1b** and **1a** radical structures, respectively. Also the obtained results reveal that the values of spin density for C3 in **1d**, **1c**, **1b** and **1a** radical structures are 0.533, 0.332, 0.291 and 0.242, respectively. Therefore, in the case of **1d** radical structure, the spin density of C6 in benzene ring decreases obviously, while the spin density of C3 increases. In addition, the spin density of O1 (0.185) in **1d** radical is distinctly lower than that of the **1a** (0.397), **1b** (0.388), and **1c** (0.372) radical structures, but the spin density of O5 decreases from **1d** (0.111) to **1a** (0.0799) radical structure. Thus, the oxygen atom in **1d** radical plays an important role in delocalizing the unpaired electrons and promoting the stability of the phenoxyl radical than in radical structure **1b**. This is the reason why the BDE and PA values of structure 1d are lower than those of the **1a**, **1b** and **1c** structures. Grisar *et al.*[47,48] designed the vitamin E analogue based on structure 1b, and also reported that the compound has an inhibition rate 1.8 times higher than that of α-tocopherol on free radical which is consistent with our theoretical results.

Table 1. Calculated BDEs, IPs, PAs, PDEs, O/RE s in (kJ mol^{-1}) and E_{HOMO} (eV) of studied structures with reducing the number of atoms in the heterocyclic ring

Structures	BDE	ΔBDE	IP	ΔIP	PA	ΔPA	PDE	ΔPDE	O/RE	ΔO/RE	E_{HOMO}
1a	309.5	0.0	676.7	0.0	1499.4	0.0	953.3	0.0	132.7	0.0	–5.23
1b	298.2	–11.3	685.7	8.9	1496.7	–2.7	941.1	–12.2	135.7	3.0	–5.21
1c	294.1	–15.4	712.0	35.2	1491.1	–8.3	906.7	–46.6	136.9	4.2	–5.42
1d	280.8	–28.7	723.8	47.0	1461.2	–38.1	877.6	–75.7	142.8	10.1	–5.45

Computed PDE and O/RE values for studied structures are reported in Table 1. The PDE value decreases from 953.0 to 877.6 kJ mol^{-1}for the structures **1a** and **1d**, respectively; while the O/RE value increases from 132.7 to 142.8 kJ mol^{-1}.

In this paper, we tried to correlate the calculated IPs with corresponding PDEs and also correlate PAs values with corresponding O/REs for **1a**, **1b**, **1c** and **1d** structures. The correlation coefficients were 0.95 and 0.98 for PA=f(O/RE) and IP=f(PDE) dependence, respectively. Obtained Eqs. (10) and (11) from these linear regressions are as follow:

$$PA\ (kJ\ mol^{-1}) = -4.0 \times O/RE\ (kJ\ mol^{-1}) + 2036.6 \quad (10)$$

$$IP\ (kJ\ mol^{-1}) = -0.63 \times PDE\ (kJ\ mol^{-1}) + 1284.8 \quad (11)$$

Obtained equation may be used to predict IP and PA values of novel antioxidant structure from their PDE and O/RE value or *vice versa*. To accelerate the discovery of novel antioxidants, considerable effort has been devoted to investigating the structure-activity relationships (SARs) for antioxidants. Furthermore, rational design strategies for antioxidants have been proposed and applied in research. As to the calculation of IPs, since relatively accurate value is sufficient to characterize the electron-donating ability of antioxidants, the combined DFT methods are adequate.[49,50] On the other hand, according to the Koopmans' theorem,[51] the energy of the highest occupied molecular orbital (E_{HOMO}) is an alternative parameter to characterize the electron–donating ability of antioxidants, which takes advantages of the simple calculation procedure that only parent molecule is calculated. E_{HOMO} is indeed widely used in antioxidant study.[52,53] The electron to be transferred from the antioxidant to the hydroxide is expected to originate from the highest occupied molecular orbital (HOMO) of the antioxidant. The highest occupied molecular orbital (HOMO), a parameter representing the molecular electron donating ability, is also a good index predicting antioxidant activity.[54,55] Along these lines, the ionization energy of the HOMO can be employed as a measure of a compound's capacity to participate in oxidant scavenging.[56] In this paper, the calculated E_{HOMO} for basic structure (**1a**) is –5.23 eV with DFT method. As a general rule, the higher the E_{HOMO}, the more active the compound is as an antioxidant.[57] The computed E_{HOMO} for **1b**, **1c** and **1d** structures are reported in Table 1. An inspection of data in Table 1 reveals that reducing the number of atoms in the heterocyclic ring from **1a** to **1d**, cause E_{HOMO} become more negative and these structures should possess lower radical trapping potential than basic structure (**1a**). In this paper, we tried to correlate calculated IPs with corresponding E_{HOMO} for **1a**, **1b**, **1c** and **1d** structures. The IP = f(E_{HOMO}) dependences for studied structures are plotted in Figure 3. The correlation coefficient reached 0.97. Obtained Eq. (12) from the linear regression is as follow:

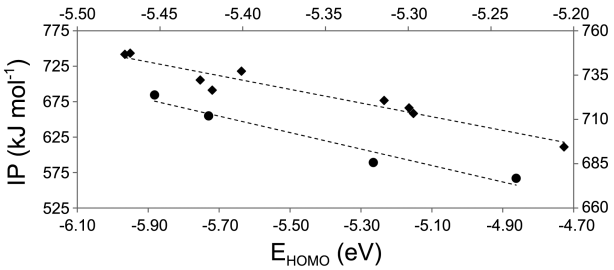


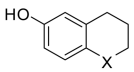
Figure 3. Dependence of IP on E_{HOMO} (eV) for structures of series 1 (circles, top *x*-axis, right *y*-axis) and structures of series 2 (squares, bottom *x*-axis, left *y*-axis).

$$IP\ (kJ\ mol^{-1}) = -0.0044 \times E_{HOMO}\ (eV) - 2.274 \quad (12)$$

Obtained equation may be used to predict IPs for novel antioxidant structure from their E_{HOMO} or *vice versa*. The negative slope of the linear dependence reflects the fact that reduces of number ring atom cause a decreases the value of IPs and absolute value of E_{HOMO}. It is very important because can be utilized in the synthesis of novel vitamin E derivatives with enhanced antioxidant properties.

Effect of Replacing Oxygen Heteroatom with Other Atoms on Reaction Enthalpies. In this section, the effect of replacing the oxygen heteroatom with other heteroatoms on antioxidant properties of basic structure of vitamin E (**2a** structure) was investigated. Accordingly, S, Se, NH, PH, AsH, CH_2, SiH_2 and GeH_2 groups were replaced with oxygen hetroatom in the basic structure. New structures obtained from replacing the oxygen heteroatom with other mentioned heteroatoms are shown in Figure 4. Finding the effect of each heteroatom on the reaction enthalpies of antioxidant mechanism can be very important and useful to synthesis novel antioxidant structures with high performance.

The computed reaction enthalpies *i.e*. BDEs, IPs and PAs for these new structures are reported in Table 1. Relative BDE, IP and PA values are also summarized in the Table 2. The vitamin E analogues based on structures **2b** and **2c** have been synthesized experimentally.[35,58] Calculated BDE, IP and PA values of structures **2b** and **2c** are lower than those of the basic structure (**2a**). The difference between BDE value of **2b** and **2c** with structure **2a** is lower than *ca.* 5 kJ mol^{-1}. Obtained result show that these difference between IP and PA value of **2b** and **2c** with **2a** structure is *ca.* 10-20 and 20-



2a (X=O), **2b** (X= S), **2c** (X=Se), **2d** (X=NH), **2e** (X= PH), **2f** (X=AsH), **2g** (X=CH_2), **2h** (X=SiH_2), **2i** (X=GeH_2).

Figure 4. Studied structures with replacing oxygen heteroatom with other atoms: X = O, S, Se, NH, PH, AsH, CH_2, SiH_2, GeH_2.

30 kJ mol^{-1}, respectively. Determination of the BDE value relating to the structure **2c** by EPR equilibration technique gave approximately 4 kJ mol^{-1} lower than that of vitamin E.[35] Kinetic studies performed by measuring oxygen uptake of the induced oxidation of styrene in the presence of an antioxidant showed that structure **2c** was a slightly stronger inhibitor than vitamin E, in agreement with the BDE values.[35] The inhibition of the azobis thermally initiated autoxidation of styrene by **2b** structure has shown that this compound trap fewer than 2.0 peroxyl radicals per molecule and that they are only slightly high reactive toward peroxyl radicals than structurally related **2a** structure.[58] Therefore, the antioxidant activities of **2b** and **2c** structure are slightly higher than basic structure of vitamin E (**2a** structure) which is in agreement with our obtained theoretical results. Calculated BDE, IP and PA values for **2d** structure is lower than that of **2a** structure. Obtained result show that these difference between BDE, IP and PA values of **2d** with **2a** structures are *ca*. 25, 65 and 45 kJ mol^{-1}, respectively. Obtained experimental results reveal that **2d** structure would be a better antioxidant than **2a** structure because nitrogen, being less electronegative than oxygen, would be better able to stabilize a neighboring radical center by conjugative delocalization of its lone pair of electrons.[11] Computed results show that the BDE and IP values for other studied structures in this section are higher than those of **2a** structure. A fundamental reason for our results can be related to the lack of lone pair of electrons in the case of CH_2, SiH_2 and GeH_2 groups. Therefore, these groups are not able to stabilize a radical or radical cation formed from first step of HAT and SPLET mechanisms.

Computed PDE and O/RE values for the studied structures are reported in Table 2. The lowest PDE values are related to structures **2i** and **2h**, while the highest PDE value is observed for structure **2d**. The structure **2d** have the lowest O/RE value and the **2i** and **2h** structure have the highest O/RE value. The PDE value increases from 906.4 to 994.6 kJ mol^{-1} for the structures **2h** to **2d**, respectively; while the O/RE value decreases from 190.2 to 97.4 kJ mol^{-1}. In this section, we tried to correlate calculated IPs with corresponding PDEs and also correlated PA values with corresponding O/REs for studied structures. The correlation coefficients reached 0.94 and 0.98 for PA = f (O/RE) and IP = f (PDE) dependence, respectively. Obtained Eqs. (13) and (14) from these linear regressions are as follow:

$$\text{PA (kJ mol}^{-1}) = -0.59 \times \text{O/RE (kJ mol}^{-1}) + 1569.6 \quad (13)$$

$$\text{IP (kJ mol}^{-1}) = -1.45 \times \text{PDE (kJ mol}^{-1}) + 2056.8 \quad (14)$$

Obtained equation may be used to predict IPs and PAs for novel antioxidant structure from their PDEs and O/REs or *vice versa*. The computed E_{HOMO} for studied structures in this section are reported in Table 2. An inspection of data in Table 2 reveals that replacing the heteroatom (O) with S, Se and NH, cause E_{HOMO} become less negative and these structures should possess higher radical trapping potential than basic structure (**2a**). Replacements of oxygen heteroatom with NH heteroatom cause a sharp decrease in the absolute value of E_{HOMO}. On country other heteroatom increased the absolute value of E_{HOMO} and cause corresponding structures have lower radical trapping potential than basic structure (**2a**). In this paper, we tried to correlate calculated IPs with corresponding E_{HOMO} for studied structures. The IP = f(E_{HOMO}) dependences for studied structures are plotted in Figure 3. The correlation coefficient reached 0.96. Obtained Eq. (15) from the linear regression is as follow:

$$\text{IP (kJ mol}^{-1}) = -95.56 \times E_{HOMO}\text{ (eV)} + 161.3 \quad (15)$$

Obtained equation may be used to predict IPs for novel antioxidant structure from their E_{HOMO} or *vice versa*. It can be employed to synthesis of new high antioxidant structures base on vitamin E.

Conclusions

In this article, the possible ways for increasing the antioxidant properties of vitamin E have been investigated with density function theory. In this article, the reaction enthalpies related to the individual steps of three antioxidant action mechanisms, HAT, SET-PT and SPLET, for novel antioxidant

Table 2. Calculated BDEs, IPs, PAs, PDEs, O/REs in (kJ mol^{-1}) and E_{HOMO} (eV) of studied structures with replacing oxygen heteroatom by other atoms: X = O, S, Se, NH, PH, AsH, CH_2, SiH_2, GeH_2

Structures	BDE	ΔBDE	IP	ΔIP	PA	ΔPA	PDE	ΔPDE	O/RE	ΔO/RE	E_{HOMO}
2a (O)	309.5	0.0	676.7	0.0	1499.4	0.0	953.3	0.0	132.7	0.0	–5.45
2b (S)	305.0	–5.5	666.3	–10.5	1477.2	–23.2	959.3	5.0	148.4	14.7	–5.23
2c (Se)	306.0	–5.5	658.4	–18.4	1467.6	–33.7	968.1	12.8	158.9	24.2	–5.16
2d (NH)	285.2	–27.3	611.2	–65.6	1460.4	–42.0	994.6	38.3	97.4	–38.3	–5.15
2e (PH)	321.4	7.9	691.3	14.6	1462.5	–40.9	950.7	–6.6	179.5	42.8	–4.73
2f (AsH)	322.3	7.8	705.7	28.9	1464.8	–39.6	937.2	–21.1	178.1	40.4	–5.72
2g (CH_2)	317.7	2.2	718.0	41.3	1441.4	–64.0	920.2	–39.1	146.8	8.2	–5.75
2h (SiH_2)	327.7	11.2	741.8	65.1	1458.1	–48.3	906.4	–53.9	190.2	50.5	–5.64
2i (GeH_2)	328.0	10.5	743.5	66.8	1460.3	–47.1	908.0	–53.3	187.3	46.6	–5.97

based on vitamin E were calculated. The novel structures that obtained from replacing methyl groups with substituents such as NH_2, OH, COOH and NHMe have greater antioxidant activity than vitamin E. Obtained results reveal that novel structure that obtained with replacing O with NH hetroatom would be a better antioxidant than vitamin E, due to nitrogen have less electronegative than oxygen and it able to stabilize radical center by conjugative delocalization comfortably. In addition, the results also reveal that reducing the number of atoms in the heterocyclic ring is a better way to synthesize novel antioxidants. The obtained results show that the IP and PA values of novel antioxidant structure can be predicted from their corresponding PDE and O/RE values, respectively. Results also reveal that IP values for studied structures can be predicted from their E_{HOMO}. This fact may be useful for the development of new better derivations as antioxidants.

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