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Exploring a possible way to synthesize novel better antioxidants based on vitamin E: A DFT study

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Abstract—The promoting effect of heterocyclic ring and heteroatom on the antioxidant properties of vitamin E has been investigated systemically by using density functional theory. The calculated results show that the heteroatom plays a more important role in promoting the antioxidant properties than the heterocyclic ring, indicating that replacing O atom by S or Se is impossible to synthesize the novel better antioxidants. Furthermore, the bond dissociation enthalpy (BDE) and ionization potential (IP) of the corresponding molecules are decreased dramatically when the O atom is replaced by NH. In addition, the calculated results also reveal that reducing the atom number of heterocyclic ring is an ideal way to synthesize novel antioxidants with better antioxidant activity than vitamin E.

Vitamin E is a well-known lipid-soluble antioxidant in biological system.[1] It acts as the chain-breaking antioxidant and protects cell membranes from oxidative degradation. The term vitamin E represents a series of structurally similar compounds, which consist of a fused heterocyclic ring and a side chain. The latter has no effect on its antioxidant activity, but serves to hold the chemically reactive 'head' in biomembranes.[2] As compared with phenol, the antioxidant activities of vitamin E mainly come from its heterocyclic ring and the heteroatom except the substituted methyl group. In order to develop novel antioxidants better than vitamin E, several efforts have been made to synthesize vitamin E analogues,[3–10] generally, there are two ways used, one is replacing heteroatom with other atom, such as selenium (Se), the other is reducing the atom number of heterocyclic ring. In this paper, the effects of the heterocyclic ring and the heteroatom on the antioxidant properties of vitamin E are investigated by density functional method, which has been testified to be a useful and economical method to investigate antioxidant mechanism of molecules,[11–13] and we also expect to search a possible way to develop vitamin E analogues with a better antioxidant activity.

The antioxidant mechanisms of phenol include hydrogen atom transfer (Eq. 1) and electron transfer (Eq. 2). The former is controlled by the bond dissociation enthalpy (BDE) of antioxidant and the latter is controlled by the ionization potential (IP) of antioxidant. The lower the BDE or IP is, the higher the hydrogen atom or electron-transfer ability will be. The BDE and IP of molecules have been calculated by a combined method labeled as ROB3LYP/6-311 + G (2d, 2p)// B3LYP/6-31G(d).[13] All investigations have been performed by using the Gaussian 03 program.[14]

$$\mathrm{ArOH} \rightarrow \mathrm{ArO}^{\cdot} + \mathrm{H}^{\cdot}$$
$$\mathrm{BDE} = E(\mathrm{ArO}^{\cdot}) + E(\mathrm{H}^{\cdot}) - E(\mathrm{ArOH}) \qquad (1)$$

$$\mathrm{ArOH} \rightarrow \mathrm{ArOH}^{\cdot+} + \mathrm{e}^{-}$$
$$\mathrm{IP} = E(\mathrm{ArOH}^{\cdot+}) - E(\mathrm{ArOH}) \qquad (2)$$

The calculated BDE of phenol by the above method is 87.57 kcal/mol, which is close to the 'best' experimental value of 87.30 kcal/mol in gas phase,[15] and also in the rang of recommended value of 86.7 ± 0.7 kcal/mol by

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Peter Mulder.[16] The BDE of 1b (Fig. 1) is 80.75 kcal/mol, in agreement with other result 81.43 kcal/mol.[17] And the BDE of **1c** (79.85 kcal/mol) is also close to the previous theoretical value of 80.24 kcal/mol[17] and the experimental result of 81.62 kcal/mol.[18]

The effects of the heterocyclic ring and the heteroatom (O atom) on vitamin E antioxidant activities have been investigated by comparing the BDE of **1b** (Fig. 1) with that of **1a** and phenol according to their differences in structure. For example, the X atom is CH_2 in the **1a**, but O in the **1b**, the differences of their antioxidant activities contributing to the effect of O atom. As shown in Figure 2, the BDE of **1b** is lower than that of phenol by 6.80 kcal/mol, it should be pointed out that the heterocyclic ring contributes to 2.41 kcal/mol, while the heteroatom (O atom) contributes to 4.39 kcal/mol, which suggests that the heteroatom (O atom) plays a more important role than the heterocyclic ring in improving the antioxidant activity of vitamin E. The O atom in vitamin E has been regarded to delocalize the unpaired electron by its p-type orbitals and improve the stability of the phenoxyl radical.[19] As for IP, the heterocyclic ring has a large reducing effect than the heteroatom (O atom). When the heteroatom (O atom) in vitamin E is replaced by other atoms, such as S and Se, the BDE is decreased slightly (Table 1). The vitamin E analogues based on **1c** and **1d** (1-thio-α-tocopherol and 1-seleno-α-tocopherol) have been synthesized experimentally,

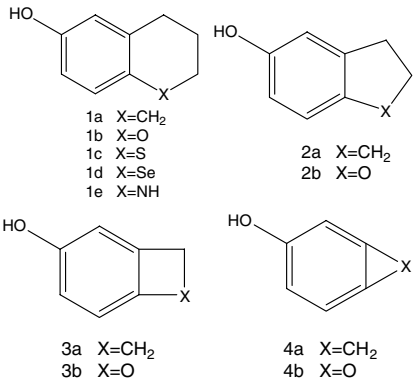

Figure 1. The structure calculated in the manuscript.

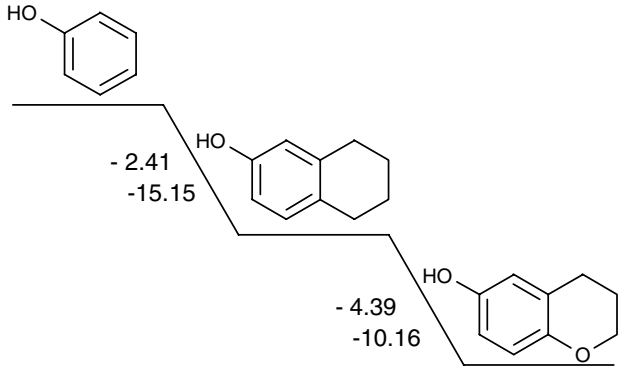

Figure 2. The differences of BDE and IP between the phenol, **1a** and **1b**.

Table 1. The BDE and IP of calculated molecules

Compound	X	BDE (kcal/mol)	IP (kcal/mol)
1a	CH_2	85.16	177.55
1b	O	80.75	167.39
1c	S	80.90	163.92
1d	Se	81.06	162.78
1e	NH	76.23	153.03
2a	CH_2	84.70	178.25
2b	O	79.85	168.59
3a	CH_2	84.61	181.60
3b	O	80.18	176.19
4a	CH_2	84.26	185.30
4b	O	76.61	181.47

and their antioxidant activities are slightly weaker than that of α-tocopherol,[10,20] which is in accordance with our theoretical results. Thus it is impossible to synthesize a novel better antioxidant with heteroatom O being replaced by S or Se. However, when the heteroatom O is replaced by NH (**1e**), both the BDE and IP are sharply reduced because the nitrogen is less electronegative than oxygen and tends to stabilize the radical formed by conjugative delocalization of its lone pair of electrons. In fact, this situation has been found by Wright.[21] Some functional groups should be adopted to improve the IPs of these kind of molecules because a lower IP will cause reaction with oxygen easily.[5] Recently, some ortho hydroxy-amino coumarin derivatives have been synthesized and demonstrated to be the strong antioxidant as compared to the ortho dihydroxy derivatives and α-tocopherol[22] our theoretical results also indicate that some

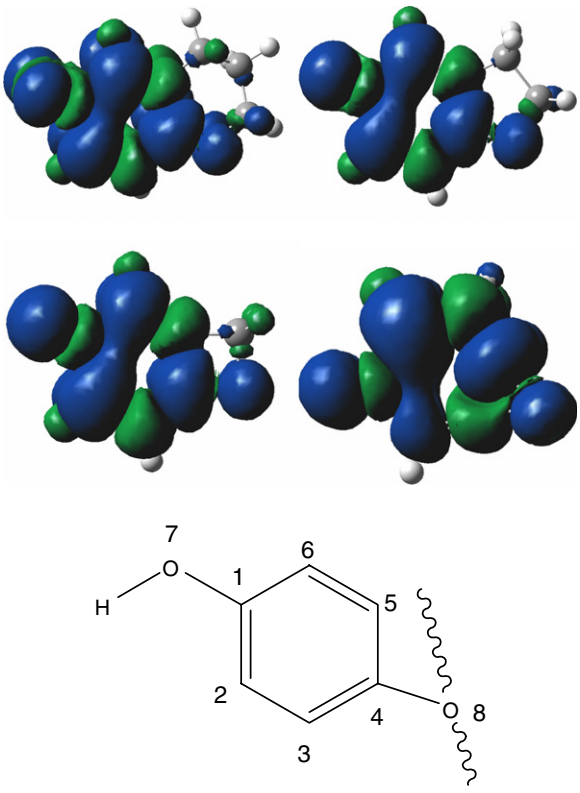

Figure 3. The spin density of **1b**, **2b**, **3b**, and **4b** and the ring number used in the manuscript.

aminophenols maintain a lower BDE and a higher IP than α-tocopherol.[23]

The heterocyclic ring also affects the antioxidant activities of vitamin E. The BDE and IP of **1b**, **2b**, **3b**, and **4b** have been calculated to investigate the effect of heterocyclic ring with different atom number. From **1b** to **4b**, the BDE decreases from 80.75 to 76.61 kcal/mol, and the IP goes up from 167.39 to 181.47 kcal/mol, indicating that the hydrogen atom donating ability increases while the electron donating ability decreases. From **1a** to **4a**, the variation of BDE and IP follows the same pattern. Ingold and co-workers designed the vitamin E analogue based on **2b**, and also reported that the compound has an inhibition rate 1.8 times higher than that of α-tocopherol on free radical,[24,25] which is consistent with our theoretical results. According to our calculated results, it is a suitable way to synthesize novel antioxidant better than vitamin E by reducing the atom number of heterocyclic ring. Because the p-type orbital of O atom in vitamin E can delocalize the unpaired electron, and then improve the stability of the phenoxyl radical, the spin density of **1b**, **2b**, **3b**, and **4b** radical has been checked. As shown in Figure 3, the spin density of the **1b**, **2b**, and **3b** radical mainly distributes on the C2, C4, and C6 of benzene ring and O7, but for the **4b** radical, the spin density of C4 in benzene ring is decreased obviously, while the spin density of C6 goes up. In addition, the spin density of O7 (0.17) in **4b** radical is distinctly lower than that of the **1b**, **2b**, and **3b** radical, but the spin density of O8 decreases from 0.10 of the **4b** radical to 0.07 of the **1b** radical. Thus, the oxygen atom in **4b** radical plays an important role in delocalizing the unpaired electrons and promoting the stability of the phenoxyl radical than in **1b** radical, this is the reason why the BDE of **4b** is lower than that of the **1b**.

Finally, the frontier orbital of calculated molecules has been analyzed further to explain the change of IPs. Table 2 shows the highest occupied molecular orbital (HOMO) and the lowest occupied molecular orbital (LUMO), HOMO-1, and LUMO-1 of **1b**, **2b**, **3b**, and **4b**. All the HOMO, HOMO-1 LUMO, and LUMO-1 decrease from **1b** to **4b**. The lower the HOMO, the weaker the molecular donating electron ability.[26] So the decreased HOMO leads to the increasing IP.

In summary, the enhancing effects of heterocyclic ring and heteroatom on the antioxidant properties of vitamin E have been investigated by using density functional theory. The calculated results show that it is impossible to synthesize the novel antioxidants by replacing O atom with S or Se. However, when the O atom is replaced by NH, the BDE and IP of molecule are decreased dramatically. In addition, the results also reveal that reducing the atom number of heterocyclic ring is a better way to synthesize novel antioxidants which are better than that of vitamin E, it is expected that the derivatives of **2b** and **4b** will be the better candidates.

Table 2. The HOMO, HOMO-1, LUMO, and LUMO-1 of **1b**, **2b**, **3b**, and **4b**

Compound	HOMO-1 (eV)	HOMO (eV)	LUMO (eV)	LUMO-1 (eV)
1b	−0.25154	−0.20491	−0.02057	−0.0029
2b	−0.2573	−0.20501	−0.02401	−0.00373
3b	−0.26649	−0.21341	−0.02953	−0.00705
4b	−0.27828	−0.21684	−0.03423	−0.01876

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