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Theoretical Elucidation on Structure–Antioxidant Activity Relationships for Indolinonic Hydroxylamines

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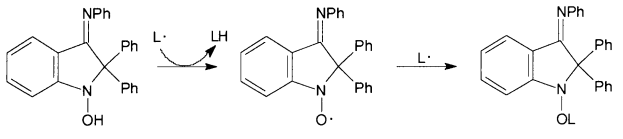
Abstract—Indolinonic hydroxylamines (IH), representing a new type of antioxidants, are comparative to α-tocopherol to protect lipids from oxidation. To elucidate the structure–activity relationship for IH, B3LYP/6-31G(d, p) method was employed to calculate the O–H bond dissociation enthalpy (BDE), a theoretical parameter to characterize the free radical scavenging activity. By constructing several model molecules, it was revealed that hydroxylamine was the key structural factor for this type of antioxidants, and substituents had little effect on the O–H BDE. If the =NR of IH was substituted by =O, its activity got lower.

Free radicals play an important role in causing many diseases and deteriorating foods. So selecting efficient antioxidants to scavenge free radicals has aroused great interest.[1] Apart from the traditionally used phenolic antioxidants, such as tocopherols and flavonoids,[2] other types of antioxidants, for example, indolinonic hydroxylamines (IH) and related aminoxyls, were also given much attention, due to their excellent free radical scavenging activity.[3] For instance, 1-hydroxy-1,2-dihydro-2,2-diphenyl-3H-indole-3-phenylimine is comparable to α-tocopherol (α-T) to protect methyl linoleate from oxidation by donating a hydrogen. And more interestingly, its succeeded radical is also a radical scavenger (Scheme 1).[3a]

Considering the wide prospect of this type of antioxidants, it is significant to elucidate their structure–activity relationships (SAR) and to answer the following questions: (i) Why IH is comparative to α-T; (ii) Which structural factor is most important for IH to reserve the antioxidant activity; (iii) Although the =O substituted indolinonic aminoxyl has been used in preventing lipid from oxidation,[3] the reduced form of this kind of compound have not been used in practice. Are they more active than the =NR substituted counterparts? Since quantum chemical calculations, especially density functional theory (DFT), has been used successfully to investigate and elucidate the SAR for phenolic antioxidants,[4] we attempt to answer the above questions by DFT calculations.

Free radical scavenging activity of phenolic antioxidants is mainly determined by the strength of the O–H bond.[5] The lower the O–H bond dissociation enthalpy (BDE), the higher the antioxidant activity. Hence, O–H BDE was used as the theoretical parameter to characterize the free radical scavenging activity of IH. To elucidate the SAR for IH is to investigate the contribution of each substituent to the O–H BDE of IH. According to the definition of O–H BDE, $BDE = H_r + H_h - H_p$, in which, H_r is the enthalpy for radical generated after H-abstraction, H_h is the enthalpy for hydrogen atom, and H_p is the enthalpy for parent molecule.

Although the density functional theory (DFT) underestimates the O–H BDE, it is generally reliable for predicting substituent effects on O–H BDEs.[6] The



Scheme 1. Mechanisms of 1-hydroxy-1,2-dihydro-2,2-diphenyl-3*H*-indole-3-phenylimine to scavenge free radicals.

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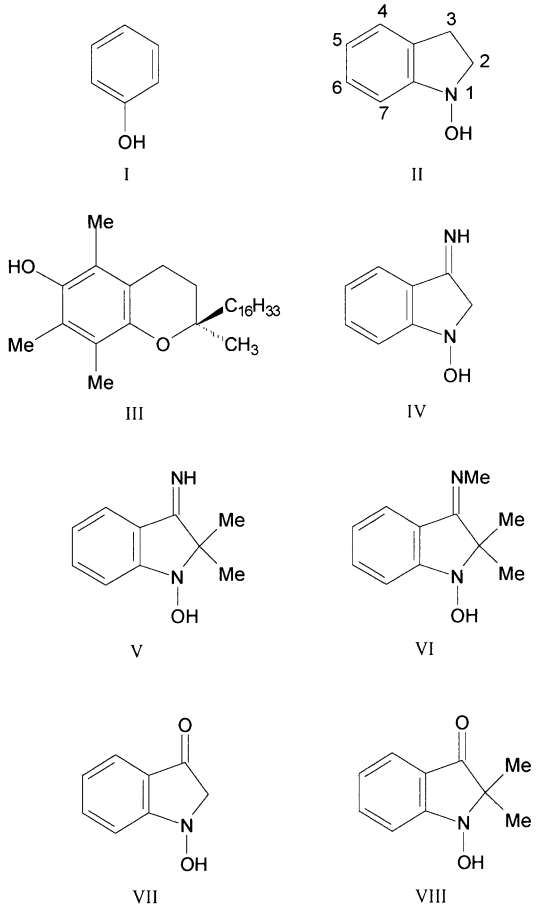
calculation procedures are as follows. The molecular geometries were optimized, firstly, by molecular mechanic method MMX,[7] and then, by semiempirical quantum chemical method AM1.[8] Finally, B3LYP/6-31G(d, p) was used for the full geometry optimization. The zero point vibrational energy corrections were scaled by a factor of 0.9805.[9] The quantum chemical calculations were accomplished by Gaussian 94.[10]

In order to investigate the contribution of each group to the O–H BDE for IH, we constructed several model indolinonic hydroxylamines (Scheme 2, II, IV–VIII). The O–H BDEs for these molecules were calculated and listed in Table 1.

The O–H BDE for phenol (I) was calculated to be 82.98 kcal/mol, identical to the value (82.8 kcal/mol) calculated by de Heer et al. with the same method.[6c] However, the O–H BDE for molecule II drops to 63.88 kcal/mol, 19.10 kcal/mol lower than that of phenol, and 8.06 kcal/mol lower than that of α-T (III). The extremely low O–H BDE of II stems from the fact that the oxygen radical derived from II is efficiently stabilized by the *p*-type lone pair on the adjacent nitrogen. According to physico-organic chemistry theory, the substitution of electron-withdrawing groups will stabilize the parent molecule and destabilize the radical, hence, enhance the O–H BDE. However, electron-donating groups have an opposite effect, and therefore, reduce the O–H BDE.[6] This is demonstrated by the O–H BDEs of molecules IV–VIII. The substitution of =NH (IV), an electron-withdrawing group, enhances the O–H BDE 0.74 kcal/mol, comparing with that of II. The substitution of methyl, an electron-donating group, results in the reduction of O–H BDE, that is, two methyls' substitution at position 2 (V) lowers the O–H BDE 2.11 kcal/mol, and one methyl's substitution at NH (VI) induces 1.14 kcal/mol reduction of the O–H BDE. As the electronic property of phenyl is comparable to that of methyl,[11] it is reasonable to speculate that the O–H BDE of 1-hydroxy-1,2-dihydro-2,2-diphenyl-3H-indole-3-phenylimine will be similar to that of molecule VI, approximately 10 kcal/mol lower than that of α-T. However, in the chemical kinetic point of view, the large steric hindrance of phenyl groups will attenuate the radical scavenging activity of 1-hydroxy-1,2-dihydro-2,2-diphenyl-3H-indole-3-phenylimine through preventing radical approaching to the hydroxyl-amino group. In short, it is understandable that the compound is comparable to α-T to scavenge free radicals and suppresses the consumption of α-T. It is also clear that the key structural factor for IH to reserve the high antioxidant activity is hydroxylamine (II), and the substituents have little effect on the activity of IH.



Scheme 2. Structures of model molecules. As the phytyl chain has little effect on the O–H BDE of α-T (III), it was replaced by methyl in the DFT calculations.

If position 3 of II is substituted by oxygen, an electron-withdrawing group, giving molecule VII, the O–H BDE gets 1.73 kcal/mol higher than that of II. Similarly, the methyls' substitution reduces the O–H BDE of VII. Moreover, it is interesting to note that the O–H BDEs of VII and VIII are ~1 kcal/mol higher than those of IV and V, consistent with the fact that =O is a stronger electron-withdrawing group than =NH. Hence, theoretically speaking, the =O substituted IH will be weaker than their =NR counterparts to scavenge free radicals.

At last, it should be noted that in the heterogeneous solutions, the antixoidant activity is determined not only by the electronic effects and steric effects of the substituents, but also by the lipophilicity of the compounds.[3b,12] Hence, the length of the side chain in IH will affect their free radical scavenging activity.

Table 1. O–H BDE of model molecules calculated by B3LYP/6-31G(d, p), $T = 298.15$ K

	H_p[a](Hartree)	H_r[b] (Hartree)	O–H BDE[c] (kcal/mol)
I	−307.4784667	−306.8353850	82.98
II	−440.2011313	−439.5895311	63.88
III	−696.0330093	−695.4081802	71.94
IV	−494.3363782	−493.7237590	64.62
V	−572.9756298	−572.3664947	62.51
VI	−612.2808604	−611.6737242	61.37
VII	−514.2161456	−513.6019479	65.61
VIII	−592.8566548	−592.2454413	63.78

[a]Enthalpy of parent molecule.
[b]Enthalpy of radical derived from parent molecule.
[c]O–H BDE = $H_r + H_h - H_p$, in which, $H_h = -0.49792$ Hartree.

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