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The ortho hydroxy-amino group: Another choice for synthesizing novel antioxidants

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Abstract—Four ortho hydroxy-amino derivatives have been designed based on the structures of flavonoids to explore the effect of the ortho hydroxy-amino group on the antioxidant properties of molecules, and their bond dissociation enthalpies (BDE), ionization potentials (IP), the highest occupied molecular orbitals (HOMO), and spin densities have been calculated. The results reveal that the ortho hydroxy-amino group plays an important role in promoting the antioxidant properties of molecules because of its lowering effect on BDE, IP, and spin density. The derivatives with ortho hydroxy-amino group show stronger antioxidant activity than the derivatives with mono hydroxy or ortho dihydroxy group. Thus, the ortho hydroxy-amino group can be used as another potential functional group to synthesize novel antioxidants as guessed.

Free radicals are ubiquitous compounds in nature and can be produced from external sources, such as exposure to X-rays, ozone, cigarette smoking, air pollution and industrial chemicals.[1–4] It has been demonstrated that free radicals can damage proteins, lipids, and DNA of bio-tissues, and cause many diseases such as atherosclerosis, pneumoconiosis, cardiovascular disease, Alzheimer, and cancer.[5–8] Antioxidants can prevent the damage caused by free radical for its free radicals scavenging activity.[9,10] Flavonoids, especially those with ortho dihydroxy group, are widely noticed antioxidants.[11,12] The ortho dihydroxy group has been regarded as one of the important groups because it can improve the antioxidant activity of flavonoids.[13–16] Recently, some ortho hydroxy-amino coumarin derivatives have been synthesized and demonstrated to have stronger antioxidant activity than the ortho dihydroxy coumarin derivatives and α-tocopherol.[17] Some theoretical and experimental results reveal that the amino group will decrease the BDE and IP of phenol, especially ortho amino,[14,18,19] therefore the ortho hydroxy-amino group may be another choice for synthesizing novel antioxidants because a low BDE or IP means a higher antioxidant activity. The flavonoids are the main antioxidants in our food,[20–23] four modes have been designed based on their structures, including phenol, phenolic acid, flavonol, and flavone, to check the effect of the ortho hydroxy-amino group on the antioxidant properties of molecular compounds in comparison with the corresponding compounds with the mono hydroxy and ortho dihydroxy group by checking the BDE, IP, HOMO, and spin density (Fig. 1).

All investigations were performed by using the Gaussian 03 program.[24] The bond dissociation energy (BDE) for O–H or N–H cleavage was calculated as the sum of total energy of the formed radical and the hydrogen atom minus the total energy of the species before hydrogen atom was dissociated (Eq. 1). A combined method labeled as ROB3LYP/6-311+G (2d, 2p)//AM1/AM1 was employed in this study to provide precise BDE.[14] The geometry was optimized by the AM1 method first, and the zero-point vibrational energy (scaled by a factor of 0.9730) was obtained by frequency calculation at the same level. Then, the single-point energy was calculated at the ROB3LYP/6-311+G (2d, 2p) level. The molecular total energy consisted of the single-point energy and

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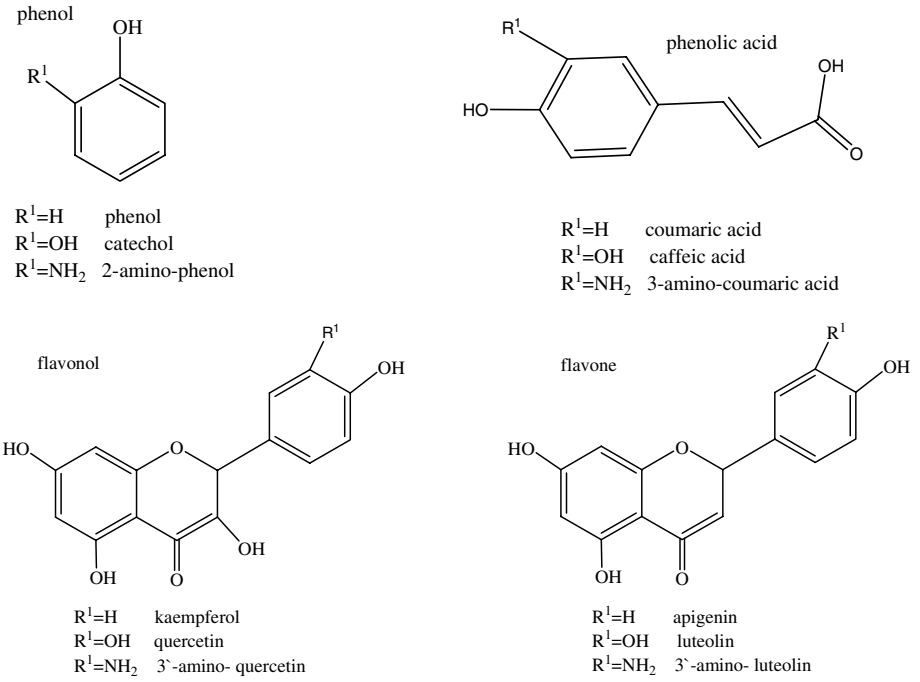

Figure 1. The structures of molecules calculated.

scaled zero-point vibrational energy. IP was calculated as the total energy of the radical species after the electron oxidation minus the total energy of the species before it was oxidized (Eq. 2).

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

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

The calculated BDE of phenol is 87.12 kcal/mol, which is close to the theoretical value of 87.10 kcal/mol[14] and the recommended value of 86.7 ± 0.7 kcal/mol by Mulder et al.[25] The calculated BDE of catechol is 78.27 kcal/mol, which is also close to the experimental value of 79.30 kcal/mol.[26] Considering the reports that the N–H bond is easily cleaved,[27,28] the N–H BDE in the modes also have been calculated. However, the calculated results reveal that the N–H BDEs of 2-amino-phenol, 3-amino-coumaric acid, 3′-amino-quercetin, and 3′-amino-luteolin are 89.94, 91.13, 91.94, and 91.23 kcal/mol, respectively, higher than the lowest O–H BDEs in the same molecule (Table 1), thus the O–H BDEs play important roles in the antioxidant activity of the calculated molecules.

As seen from Table 1, the BDEs of the mono hydroxy derivatives, including the phenol, the caffeic acid, the kaempferol, and the apigenin, are all above 84.0 kcal/mol, so it is difficult for them to donate H-atom. For the ortho dihydroxy derivatives, the BDEs of four compounds are in the range of 76.00–79.00 kcal/mol, lower than those of the corresponding mono hydroxy derivatives, but close to the 77.3 kcal/mol[29] of α-tocopherol. The ortho dihydroxy group is reported to be able to promote the H-atom-donating ability by the intramolecular hydroxy bond, which can decrease the BDE of parent molecule and stabilize the radical formed after H-atom has been abstracted.[13–16] For example, the BDE of phenol is 87.12 kcal/mol, however, the BDE of catechol is decreased to be 78.27 kcal/mol, the other calculated compounds also show the same way. One can find that all the BDEs of derivatives with the ortho hydroxy-amino group vary in a narrow range, from 74.00 kcal/mol to 75.74 kcal/mol, and not only lower than these of the derivatives with ortho dihydroxy group and mono hydroxy group, but also lower than that of α-tocopherol (77.3 kcal/mol[29]). Thus, the ortho hydroxy-amino group has a large eliminating effect on the BDE of calculated molecules.

Both IP and HOMO are used to determine the electron-donating ability of a molecular. A low IP or a high HOMO reflects a strong ability to donate the electrons. Based on our calculated results, the IP's order from low to high corresponds to the derivatives with hydroxy-amino group, the derivatives with ortho dihydroxy group, and the derivatives with mono hydroxy group. Correspondingly, the HOMO varies in the opposite way. For example, the phenol has the highest IP and the lowest HOMO, however, the 2-amino phenol has the lowest IP and the highest BDE. This indicates that the derivatives with ortho hydroxy-amino group have higher electron-donating ability than the other derivatives. The ortho hydroxy group also can improve the electron-donating ability of the calculated compounds, but the ability is weaker than that of the ortho hydroxy-amino group. There are reports that the substitution of phenols by electron-drawing groups (e.g., $-NH_2$) will

Table 1. The scaled zero-point vibrational energy (zpve), single-point energy (spe) and O–H BDE of calculated derivatives in gas phase at 298.15 K

Species	zpve (Hartree)	spe (Hartree)	Total energy (Hartree)	O–H BDE (kcal/mol)
Phenol	0.106963	−307.569056	−307.464981	
Phenol radical	0.093084	−306.919060	−306.828489	87.12
Catechol	0.11127	−382.818979	−382.710714	
Catechol radical	0.098376	−382.184060	−382.088340	78.27
2-Amino-phenol	0.123086	−362.944460	−362.824697	
2-Amino-phenol radical	0.111145	−362.314497	−362.206353	75.74
Coumaric acid	0.157097	−573.633234	−573.480379	
Coumaric acid radical	0.142687	−572.985451	−572.846617	85.41
Caffeic acid	0.161337	−648.882433	−648.725453	
Caffeic acid radical	0.147818	−648.249666	−648.105841	76.53
3-Amino coumaric acid	0.174348	−629.010417	−628.840776	
3-Amino coumaric acid radical	0.160612	−628.381161	−628.224886	74.20
Kaempferol	0.234288	−1029.293389	−1029.065427	
Kaempferol radical	0.220138	−1028.647071	−1028.432877	84.65
Quercetin	0.238486	−1104.542620	−1104.310574	
Quercetin radical	0.225177	−1103.910314	−1103.691217	76.37
3′-Amino-quercetin	0.25152	−1084.670340	−1084.425611	
3′-Amino-quercetin radical	0.237942	−1084.040324	−1083.808806	74.77
Apigenin	0.229733	−954.043672	−953.820142	
Apigenin radical	0.215321	−953.393682	−953.184175	86.80
Luteolin	0.233951	−1029.292820	−1029.065185	
Luteolin radical	0.220519	−1028.658517	−1028.443952	77.55
3′-Amino-luteolin	0.246946	−1009.421329	−1009.181051	
3′-Amino-luteolin radical	0.233353	−1008.792533	−1008.565481	74.00

decrease the IPs of original molecules, and cause reaction with oxygen easily,[30,31] but this reaction will happen only when the IP drops very low. Our calculated results reveal that all IPs of derivatives with the ortho hydroxy-amino group are above 160.00 kcal/mol, which is higher than that of α-tocopherol (154.90 kcal/mol)[32] (Table 2).

The spin density is an important parameter to characterize the stability of free radicals, because the energy of a free radical can be efficiently decreased if the unpaired electrons are highly delocalized through the conjugated system. Table 3 lists the spin density of O-atom after the H-atom connected being abstracted in each radical. The delocalization effect of ortho hydroxy-amino group is stronger than that of the ortho dihydroxy and mono hydroxy group, because the spin density of O-atom in the radical with hydroxy-amino group is lower than that in the radical with ortho dihydroxy group and mono hydroxy group.

Based on above analysis, both the hydroxy-amino group and the ortho dihydroxy group can improve the H-atom and electron-donating ability of the calculated molecules. It has been reported that the ortho dihydroxy group can improve the antioxidant activity of flavonoids by forming an intramolecular hydroxy bond, which can decrease the BDE and IP of the parent molecule, and increase the stability of radical.[13–16] For the ortho hydroxy-amino group, there also exists an intramolecular hydroxy bond, which is weaker than that between the ortho dihydroxy groups either in the parent molecule or in the corresponding radical, because it has a longer bond length and a bigger bond angle (data not show), so the intramolecular hydroxy bond has a less effect on antioxidant properties of derivatives with ortho hydroxy-amino group. However, the electronic effect of amino group substituted on the ortho position of phenol is higher than that of hydroxy group,[14] thus the lowering effect of the ortho hydroxy-amino group on BDE and IP

Table 2. The IP and HOMO of calculated derivatives in gas phase at 298.15 K

Species	IP (kcal/mol)	HOMO (Hartree)
Phenol	192.29	−0.2337
Catechol	184.40	−0.2232
2-Amino-phenol	166.35	−0.2148
Coumaric acid	194.56	−0.2378
Caffeic acid	181.09	−0.2331
3-Amino coumaric acid	169.78	−0.2187
Kaempferol	174.23	−0.2203
Quercetin	166.53	−0.2190
3′-Amino-quercetin	160.00	−0.2102
Apigenin	178.40	−0.2331
Luteolin	173.42	−0.22980
3′-Amino-luteolin	167.87	−0.2196

Table 3. The calculated spin density of O-atom after H-atom connected being abstracted in each radical in the gas phase at 298.15 K

Species	Spin density
Phenol radical	0.309619
Catechol radical	0.268594
2-Amino-phenol radical	0.242568
Coumaric acid radical	0.217164
Caffeic acid radical	0.205983
3-Amino coumaric acid radical	0.187862
Kaempferol radical	0.213535
Quercetin radical	0.206627
3′-Amino-quercetin radical	0.190283
Aapigenin radical	0.222387
Luteolin radical	0.219775
3′-Amino-luteolin radical	0.20049

of molecule contributes to the cooperation of the intramolecular hydroxy bond and electronic effect. The antioxidant activity has a functional dependence on the BDE and IP, thus all derivatives with the ortho hydroxy-amino group have a stronger antioxidant activity than the corresponding mono hydroxy or ortho dihydroxy derivatives. Based on above results, the ortho hydroxy-amino group can be used as another potential functional group to synthesize novel antioxidants.

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