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# 1, 4-Pyrone Effects on O-H Bond Dissociation Energies of Catechols in Flavonoids: A Density Functional Theory Study

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**Abstract:** Through B3LYP/6-31G** calculations, the 1, 4-pyrone effects on O-H bond dissociation energies (BDEs) of catechols in rings A or B of flavonoids were investigated. For the catechol in ring A, although 1, 4-pyrone enlarged the conjugation system, its electron-withdrawing property increased the O-H BDE ~ $3 \times 4.184$ kJ/mol compared with that of catechol. However, for the catechol in ring B, 1, 4-pyrone was poorly conjugated with the moiety, and therefore, had little effect on the O-H BDE.

**Keywords:** Antioxidant, density functional theory, flavonoid, O-H bond dissociation energy, structure-activity relationships.

In recent years, there has been growing interest in selecting efficient antioxidants with low toxicity to reduce the damage of free radicals. Among these antioxidants, flavonoids have been paid much attention, owing to their excellent antioxidative and pharmacological activities[1].

Up to now, many efforts have been given to summarize the structure-activity relationships (SAR) for flavonoids. It has been widely accepted that two structural factors are critical for flavonoids to enhance their free radical scavenging activities. Firstly, a catechol moiety is necessary[2,3]. Secondly, a 2, 3-double bond in conjugation with the 4-oxo function in ring C, namely, a 1, 4-pyrone moiety, is also helpful[2,3]. The first factor was understood by the fact that the catechol radical generated after the hydrogen abstraction was stabilized by the electron-donating effect of *ortho* OH and the intramolecular hydrogen bond (IHB)[4]. The second factor was considered stemming from the good conjugation between the rings A, B and C[3,5].

However, there still exist some opposite demonstrations about the 1, 4-pyrone effect. For example, catechin (**Scheme 1**) is more active than luteolin (**Scheme 1**), though the latter is better conjugated[6]. Moreover, according to the above mentioned SAR, xanthonoids, such as chinonin (**Scheme 1**), would be more active than other flavonoids

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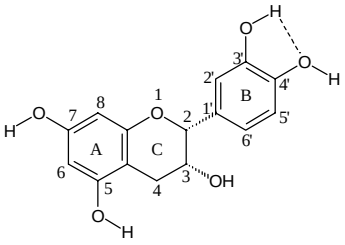
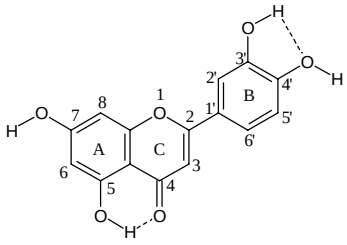
to scavenge free radicals, due to its better conjugation between rings A, B and C. But in fact, chinonin is not a good free radical scavenger at all[7]. Apparently, there exist some confusions in the understanding of the 1, 4-pyrone effect in the SAR of flavonoids. Since quantum chemical calculations have been used effectively to elucidate the SAR for antioxidants[8-10], in this letter we attempt to investigate the 1, 4-pyrone effect by the calculations of the density functional theory (DFT).

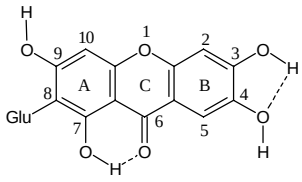
**Scheme 1** Molecular structures of several flavonoids



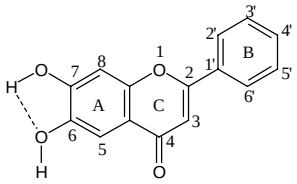
Catechin



Luteolin



Chinonin



6,7-Dihydroxyflavone

The molecular geometries were optimized, firstly, by molecular mechanic method MMX[11], and then, by semiempirical quantum chemical method AM1[12]. Finally, DFT method B3LYP/6-31G** was used for the full geometry optimization. The quantum chemical calculations were accomplished by Gaussian 94.

**Results and Discussion**

As the free radical scavenging activity of the phenolic antioxidants can be characterized by the O-H bond dissociation energy (BDE)[13-15], the effect of 1, 4-pyrone on free radical scavenging activity could be elucidated by its effect on O-H BDEs of flavonoids. We focus the study on 1, 4-pyrone's effect on O-H BDEs of catechols in flavonoids. Moreover, two kinds of structures of catechols, *i.e.*, catechol in ring A and catechol in ring B have been studied (**Scheme 2**).

According to the implication of O-H BDE, the parameter is governed by two factors, the stabilities of parent molecule (SPM) and phenoxy radical (SPR). Three isodesmic reactions were constructed to calculate the relative O-H BDE, the SPR, and the SPM for catechols[17]. The effectiveness of the isodesmic method has been evaluated by Wu and Zhang[16,17].

*1, 4-Pyrone effect on O-H BDE of catechol in ring A*

The O-H BDEs for molecules **I** and **II** (**Scheme 2, Table 1**) indicate that the 1, 4-pyrone increases the O-H BDE 2.84 or 2.64 × 4.184 kJ/mol compared with that of catechol. For molecule **I**, the increasing effect of 1, 4-pyrone on O-H BDE not only arises from destabilizing the radical, but also from stabilizing the parent molecule. However, for molecule **II**, the increasing effect mainly comes from destabilizing the radical. Although the SPRs or SPMs for **I** and **II** are much different, the relative O-H BDEs are similar to each other. Hence, the free radical scavenging effects of the two kinds of hydroxyls are similar as well.

**Scheme 2** Structures of model molecules

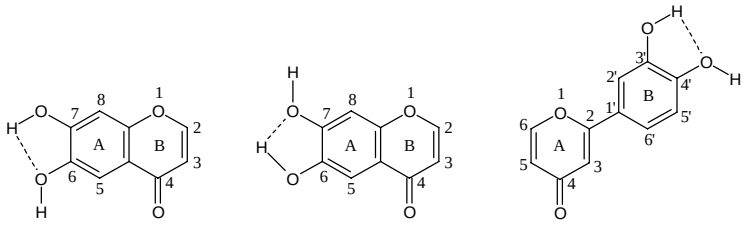



**Table 1** Relative O-H BDE, SPR and SPM ( × 4.184 kJ/mol) for catechols

| Molecules | Relative O-H BDE [a] | SPR [b] | SPM [c] |
|---|---|---|---|
| **I** [d] | –2.84 | –1.39 | 1.45 |
| **II** [e] | –2.64 | –2.98 | –0.34 |
| **III (planar)** [f] | 0.09 | 0.58 | 0.49 |
| **(twisted)** [g] | -0.006 | | |

[a] Calculated according to Eq. 4[17]. [b]Calculated according to Eq. 5[17]. [c]Calculated according to Eq. 6[17]. [d]Data for 6-OH. [e] Data for 7-OH. [f]Data for 4′-OH. Rings A and B are restricted in the same plane. [g]Data for 4′-OH. rings A and B are twisted to the natural angle for 20°. In this case, the isodesmic method to calculate the SPR and SPM is invalid, because the stereo-structures for the parent molecule and free radical are not identical.

*1, 4-Pyrone effect on O-H BDE of catechol in ring B*

To evaluate the 1, 4-pyrone effect on O-H BDE of ring B, the relative O-H BDEs for two conformations of molecule **III** (**Scheme 2**), planar and twisted, were calculated (**Table 1**). The conformation for the radical is planar, due to the conjugation between rings A and B. But the natural conformation for parent **III** is twisted, due to the steric effect between rings A and B (**Table 1**). Hence, the O-H BDE for planar **III** is a little lower than that for twisted **III**. And the difference between the two O-H BDEs, 0.096 × 4.184 kJ/mol, reflects the steric effect between rings A and B of the parent **III**. Owing to the poor conjugation between 1, 4-pyrone and catechol in ring B, the 1, 4-pyrone has little effect on the O-H BDE (**Table 1**), implying that flavonoids with catechol in ring B will be more active than that with catechol in ring A to scavenge free radicals, which really has

been observed in experiments[18,19].

In brief, although 1, 4-pyrone enlarges the conjugation system of flavonoids, it is not beneficial to reduce the O-H BDE, due to its electron-withdrawing property, and thus, it is unlikely favorable to enhance the free radical scavenging activity of flavonoids.

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