Substituent Effects on O–H Bond Dissociation Enthalpies and Ionization Potentials of Catechols: A DFT Study and Its Implications in the Rational Design of Phenolic Antioxidants and Elucidation of Structure – Activity Relationships for Flavonoid Antioxidants**

Hong-Yu Zhang,*[a] You-Min Sun,[b] and Xiu-Li Wang[c]

Abstract: Density functional theory (DFT) on B3LYP/6-31G(d,p) level was employed to investigate the substituent effects on O–H bond dissociation enthalpies (BDEs) and ionization potentials (IPs) of catechols. It was revealed that the *ortho* hydroxyl of catechol was effective for the reduction of the O–H BDE; however, the group had little influence on the IP. The *para* substituent effects upon O–H BDEs and IPs for catechols were roughly the same as those for monophenols, and this gave the catechol moiety more potential than monophenol to be used as a lead compound in rational design of phenolic antioxidants. In addition, the 1,4-pyrone effects on O–H BDEs of catecholic rings A or B of flavonoids were also investigated. Although 1,4-pyrone extended the conjugation system of flavonoids, it was not beneficial to reduce the O–H BDE as a result of its electron-withdrawing property. Thus, 1,4-pyrone was unlikely to be favorable to enhance the H-abstraction activity of flavonoids.

Keywords: antioxidants · bond dissociation enthalpy · catechols · density functional calculations · structure – activity relationships

Introduction

Free radicals play a significant role in causing many diseases, deteriorating foods, and degrading chemical materials. Hence, in recent years, there has been growing interest in selecting efficient antioxidants with low toxicity to reduce the damage of radicals.[1–4] Furthermore, rational design strategies based on structure – activity relationships (SAR) have been proposed to direct the synthesis and selection of novel antioxidants.[5]

[a] Prof. H.-Y. Zhang
Laboratory for Computational Biology
Shandong University of Technology
Zibo 255049 (P.R. China)
Fax: (+86) 533-2780271
E-mail: zhanghy@sdut.edu.cn

[b] Dr. Y.-M. Sun
Institute of Theoretical Chemistry
Shandong University, Jinan 250100 (P.R. China)

[c] X.-L. Wang
Department of Chemistry
Shandong Teachers' University
Jinan 250014 (P.R. China)

[**] Abbreviations: α-T, α-tocopherol; BDE, bond dissociation enthalpy; DFT, density functional theory; ED, electron-donating; EW, electron-withdrawing; IHB, intramolecular hydrogen bond; IP, ionization potential; SAR, structure – activity relationship; ZPVE, zero-point vibrational energy.

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

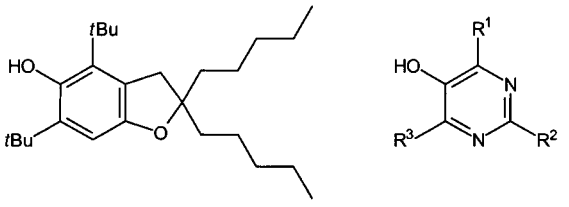
For the phenolic antioxidants, which are widely used in many fields, it is commonly accepted that the key factors that help to enhance the antioxidative potency include the following.

1) A relatively low O–H bond dissociation enthalpy (BDE),[6–17] which facilitates the H-abstraction reaction between antioxidant and radical.
2) A relatively high ionization potential (IP),[16, 17] which decreases the electron-transfer rate between antioxidant and oxygen, and thus, reduces the pro-oxidative potency of the antioxidant.
3) A stable radical of the antioxidant generated after the H-abstraction reaction,[18, 19] which decreases the toxicity of antioxidant.
4) An appropriate solubility,[20, 21] which improves the mobility of the antioxidant between membranes and lipoprotein.

Accordingly, several attempts have been made to design novel antioxidants with high activity and low toxicity. For instance, Niki and co-workers designed and synthesized an α-tocopherol (α-T) analogue, BO-653 (Scheme 1),[22] which was demonstrated, as expected, to be an inhibitor of low-density lipoprotein oxidation. Pratt and co-workers designed and synthesized 5-pyrimidinols (Scheme 1),[17] which were better radical scavengers than α-T.

However, up to now, most of the rationally designed antioxidants have been monophenolic compounds. Considering the fact that a catechol moiety is necessary for most

  0947-6539/03/0902-0502 $ 20.00+.50/0



BO-653 5-pyrimidinols

Scheme 1.

natural antioxidants to enhance their activity,[23–30] we think this moiety may be a good lead structure for the rational design of phenolic antioxidants. According to Wright and coworkers' theory,[16] to design an optimum synthetic antioxidant, for example, for a given biological role, one must consider the BDE and the IP first. Hence, to evaluate whether catechol is a good lead structure, we will have to investigate the substituent effects on O–H BDEs and IPs of catechols. Moreover, this will also be helpful to elucidate the SAR for natural antioxidants, such as flavonoids that usually contain a catechol moiety.

Calculation Methods

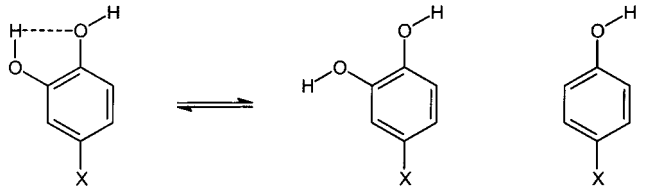
As a fundamental chemical parameter,[31] there have been several types of theoretical methods to estimate O–H BDE. The first is through the additivity rule. Although this is convenient to estimate the O–H BDEs for monophenols,[16, 32] it has not been demonstrated generally as effective for catechols. The second is through semiempirical quantum chemical calculations by means of MNDO, AM1, and PM3 methods.[9–11, 14, 33] The third is through ab initio or density functional theory (DFT) calculations.[10, 14–17, 34–40] Although DFT methods underestimate the absolute O–H BDE, they are generally reliable for predicting the relative O–H BDE,[14–17, 34–40] except for *ortho tert*-butyl-substituted phenols.[16, 40] In addition, DFT methods are also effective to calculate IPs.[16, 17, 41] Considering the accuracy and convenience of DFT methods, we employed the B3LYP function[42–44] on the basis set of 6-31G(d,p) in this paper to do calculations. The procedures were as follows. The molecular geometries were optimized firstly by the molecular mechanic method MMX[45] and then by the semiempirical quantum chemical method AM1.[46] Finally, B3LYP/6-31G(d,p) was used for the full geometry optimization in the gas phase. The zero-point vibrational energies (ZPVEs) and the vibrational contribution to the enthalpy were scaled by a factor of 0.9805.[47] The quantum chemical calculations were accomplished by Gaussian 94.[48]

Abstract in Chinese:

用密度泛函理论的B3LYP方法在6-31G(d,p)基组上探讨了儿茶酚 O–H 解离能和电离势的取代基效应. 发现儿茶酚的邻位酚羟基可有效降低O–H解离能, 但对电离势影响不大, 而且对位取代基对儿茶酚 O–H 解离能和电离势的影响与对单酚相应参数的影响相近. 这使得儿茶酚作为先导化合物在抗氧化剂的合理设计方面比单酚更有优势. 此外, 还探讨了 1,4-吡喃酮对黄酮类化合物 A 环和 B 环中儿茶酚 O–H 解离能的影响. 发现虽然 1,4-吡喃酮扩展了黄酮类化合物的共轭体系, 但该基团的吸电子性质使其不利于降低O–H解离能, 因此1,4-吡喃酮不能提高黄酮类抗氧化剂的抽氢反应活性.

Results and Discussion

The total electronic energies, ZPVEs, and thermal corrections to energies for *para*-substituted monophenols and *para*-substituted catechols in different states (Scheme 2) were calculated and listed in the Supporting information. Accordingly, O–H BDEs and IPs for monophenols, and O–H BDEs, IPs, and intramolecular hydrogen bond (IHB) enthalpies for catechols were calculated and listed in Table 1.



p-substituted catechol in different states *p*-substituted phenol

Scheme 2.

O–H BDE and IP of catechol: As shown in Table 1 and Scheme 3, the O–H BDE for phenol is calculated to be 82.83 kcal mol^{-1}, identical to the value calculated by de Heer et al., 82.8 kcal mol^{-1}.[36] The O–H BDE of catechol (**1**) is 10.01 (82.83 – 72.82) kcal mol^{-1} lower than that of phenol, in agreement with the *ortho*-hydroxyl effect on O–H BDE estimated previously.[49, 50] Taking into account that α-T has an O–H BDE of 10 – $\approx$ 12 kcal mol^{-1} lower than that of phenol,[17] we assume that **1** would be comparable with α-T to scavenge free radicals. In fact, many radical-scavenging experiments indicated that flavonoids with a catechol moiety in ring B were indeed comparable with α-T.[25, 26]

However, recently, employing EPR equilibration techniques, the O–H BDE of 3,5-di-*tert*-butylcatechol was determined to be $\approx$1 kcal mol^{-1} higher than that of α-T.[51] Consequently, the *ortho*-hydroxyl effect was estimated to be only – 4.6 kcal mol^{-1}. But taking into account that 3,5-di-*tert*-butylcatechol was three times better than α-T at scavenging 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals in nonpolar solvent,[52] the experimental result is not reasonable. We think the discrepancy arises from the fact that the EPR equilibration technique is not appropriate to determine O–H BDEs for intramolecular hydrogen-bonded molecules at all.

The essence of the EPR equilibration technique is to determine the equilibrium constant for the hydrogen atom transfer reaction between phenol and the corresponding phenoxyl radical [Eq. (1)].

$$ArOH + Ar'O^{\cdot} \rightleftharpoons ArO^{\cdot} + Ar'OH \quad (1)$$

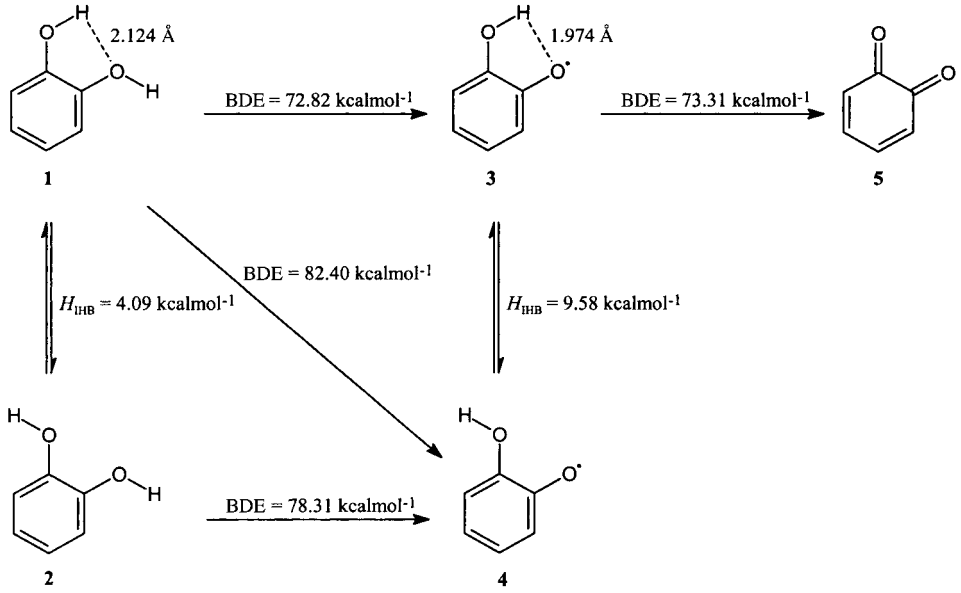
Apparently, the effectiveness of the EPR equilibration technique depends on two assumptions. First, the H-abstraction reaction is a one-step reaction. Second, the entropy of the reaction can be neglected. Both assumptions are suitable for monophenols[32, 53] but questionable for polyphenols. As shown in Scheme 4, the H-abstraction reaction pertinent to 3,5-di-*tert*-butylcatechol is not a one-step process, and thus, the free-energy variation for the overall reaction cannot

  0947-6539/03/0902-0503 $ 20.00+.50/0

Table 1. O–H BDEs, IPs, and IHB enthalpies for substituted catechols and O–H BDEs and IPs for monophenols [kcal mol^{-1}] [T = 298.15 K].

X	BDE_{cat}[a]	BDE_{ph}[b]	IP_{cat}[c]	IP_{ph}[d]	H_{IHBp}[e]	H_{IHBr}[f]	H_{IHB}[g]	C_p[h]	C_r[i]	σ_p^+[60]	F[60]	R^+[60]
H	72.82	82.83	175.48	184.85	4.09	9.58	5.49	−0.5946	−0.5299	0	0	0
Me	−1.52	−1.81	−5.62	−8.20	4.10	9.72	5.62	−0.5968	−0.5364	−0.31	0.01	−0.32
F	−1.34	−1.89	1.90	−1.09	4.79	9.76	4.97	−0.5966	−0.5304	−0.07	0.45	−0.52
Cl	−0.23	−0.62	2.57	−0.74	4.06	9.48	5.42	−0.5922	−0.5260	0.11	0.42	−0.31
OH	−4.40	−5.06	−9.58	−14.58	4.88	10.70	5.82	−0.6016	−0.5442	−0.92	0.33	−1.25
OMe	−4.75	−5.12	−14.02	−19.18	4.76	10.69	5.93	−0.6019	−0.5482	−0.78	0.29	−1.07
SH	−2.25	−2.90	−8.12	−13.93	4.41	10.13	5.72	−0.5954	−0.5373	−0.03	0.3	−0.33
SMe	−4.00	−3.87	−15.27	−21.50	3.92	10.45	6.53	−0.5970	−0.5442	−0.6	0.23	−0.83
NH_2	−7.21	−8.23	−22.19	−29.42	4.54	10.74	6.20	−0.6038	−0.5567	−1.3	0.08	−1.38
NMe_2	−8.27	−8.93	−29.55	−37.70	4.49	10.82	6.33	−0.6030	−0.5641	−1.7	0.15	−1.85
CHO	2.04	2.37	8.93	8.01	3.02	8.38	5.36	−0.5823	−0.5146	0.73	0.33	0.4
CN	2.10	2.22	12.57	10.82	3.68	9.01	5.33	−0.5839	−0.5140	0.66	0.51	0.15
NO_2	3.69	4.21	16.38	18.18	3.27	8.41	5.14	−0.5810	−0.5094	0.79	0.65	0.14
CF_3	2.15	3.01	8.72	9.54	3.26	8.94	5.68	−0.5880	−0.5203	0.61	0.38	0.23

[a] O–H BDEs of catechols. BDE = $H_r + H_h - H_p$, in which, H_r is the enthalpy for radicals generated after H abstraction, H_h is the enthalpy for the hydrogen atom, −0.49792 hartrees, and H_p is the enthalpy for the parent molecule. The first value is absolute O–H BDE for catechol, and the others are relative to the first value. [b] O–H BDEs of monophenols. BDE = $H_r + H_h - H_p$, in which, H_r is the enthalpy for radicals generated after H abstraction, H_h is the enthalpy for the hydrogen atom, −0.49792 hartrees, and H_p is the enthalpy for the parent molecule. The first value is absolute O–H BDE for phenol, and the others are relative to the first value. [c] Ionization potentials of catechols. IP = (TE_c + $ZPVE_c$ × 0.9805) − (TE_P + $ZPVE_P$ × 0.9805), in which, TE_c is the total energy for the cation radical, $ZPVE_c$ is the zero-point vibrational energy for the cation radical, TE_P is the total energy for the parent molecule, and $ZPVE_p$ is the zero-point vibrational energy for the parent molecule. The first value is the absolute IP for catechol, and the others are relative to the first value. [d] Ionization potentials of monophenols IP = (TE_c + $ZPVE_c$ × 0.9805) − (TE_P + $ZPVE_P$ × 0.9805), in which, TE_c is the total energy for the cation radical, $ZPVE_c$ is the zero-point vibrational energy for the cation radical, TE_P is the total energy for the parent molecule, and $ZPVE_p$ is the zero-point vibrational energy for the parent molecule. The first value is the absolute IP for phenol, and the others are relative to the first value. [e] IHB enthalpies in parent catechols. [f] IHB enthalpies for catecholic radicals derived from H abstraction. [g] IHB contributions to O–H BDEs of catechols: $H_{IHBr} - H_{IHBp}$. [h] Net charge of O1 in the parent catechol. [i] Net charge of O1 in the catecholic radical.



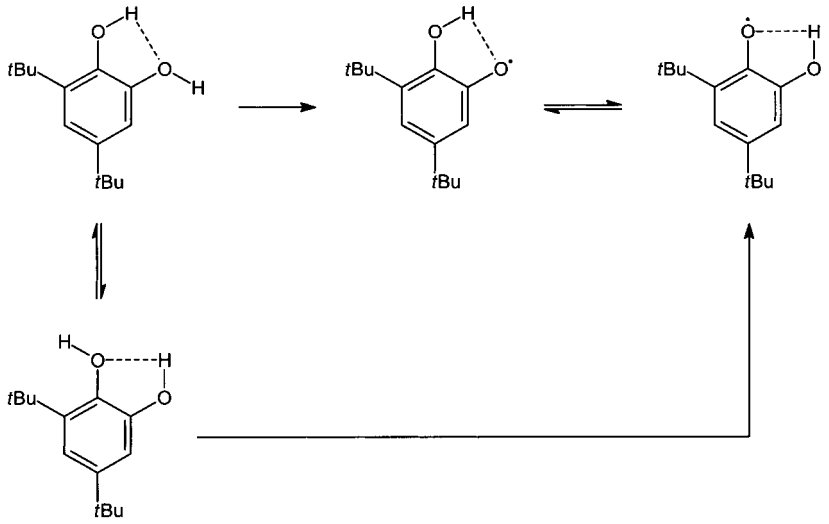
Scheme 3.

represent the O–H BDE. On the other hand, there is not any evidence supporting the assumption that the entropy variations for the H-abstraction reactions of catechols are similar to those of monophenols. As DFT methods are not accurate at calculating entropy, a detailed investigation on this subject will be accomplished by higher level calculations and will be published elsewhere.

A thermodynamic scheme for catechol (Scheme 3) indicates that the O–H BDE of **1** is determined by two kinds of substituent effects, the IHB effect and the *ortho*-hydroxyl electronic effect, which contribute 5.49 (9.58 – 4.09) kcal mol^{-1} and 4.52 (82.83 – 78.31) kcal mol^{-1} to reduce the O–H BDE, respectively. The latter effect is rather simple and just results from the electron-donating property of the OH group. However, the former effect is complicated, which arises from the higher IHB enthalpies in **3** than in **1**. The IHB enthalpy in **1** was estimated to be 3.6 – ≈4.0 kcal mol^{-1},[16, 54] similar to the IHB enthalpy in *ortho*-methoxyl phenol, 4.4 kcal mol^{-1}.[36] The IHB enthalpy in **3** was estimated to be 8.0 – ≈8.9 kcal mol^{-1} by theoretical calculations,[16, 54, 55] and higher than 9.1 kcal mol^{-1} from the experimental determination.[56] The higher IHB enthalpy pertinent to **3** may result from the fact that the hydrogen bond length in **3**, 1.974 Å, is much shorter than that in **1**, 2.124 Å. Evidently, the previous and present results are consistent with one another. However, the IHB enthalpy in **3** determined by the EPR equilibration technique was only 4.4 kcal mol^{-1},[51] much lower than the above results, which also suggests the equilibration technique is questionable.

On the other hand, the O–H BDE for **3**, namely the second O–H BDE for **1**, is 73.31 kcal mol^{-1}, similar to the first O–H BDE of **1**, and this suggests both hydrogens of **1** are readily abstracted in the schemed sequence. Support for this comes from the experimental finding that in the radical scavenging process, flavonoids with a catecholic ring B finally form a

0947-6539/03/0902-0504 $ 20.00+.50/0 *Chem. Eur. J.* **2003**, *9*, No. 2



Scheme 4.

quinone structure by donating two electrons and two protons.[57] As **5** is not a radical at all, the radical toxicity induced from **3** could be neglected to a certain extent.

It is also interesting to note that although the O–H BDE of catechol is comparable with that of α-T, the IP of catechol (9.37 kcal mol^{-1} lower than that of phenol) is much higher than that of α-T.[58] This indicates the *ortho* hydroxyl of catechol is efficient at reducing the O–H BDE, but has little influence on the IP.

Substituent effects on O–H BDEs and IPs of catechols: It is well known that electron-donating (ED) groups reduce the O–H BDEs and IPs for monophenols, and electron-withdrawing (EW) groups have an opposite effect.[16, 17, 34–40] It is also observed for *para*-substituted catechols that the O–H BDEs and IPs correlate well with the Brown parameter σ_p^+ (Table 1, Figures 1 and 2).[59, 60] It is noteworthy that although the substituent effects on O–H BDEs of catechols are slightly less than those for monophenols, the trends of both effects are similar to each other (Figure 1). Thus, it seems the existence of an IHB has little influence on the substituent effects on O–H BDEs for phenols. This is a result of the fact that ED groups increase and EW groups reduce the net charge of O1 in catechols and their radicals simultaneously (Table 1). Hence, ED groups strengthen and EW groups weaken the IHBs of catechols and their radicals as well, which induces the IHB effects to offset each other, and the IHB contributions to O–H BDEs only vary within ± 1 kcal mol^{-1} (Table 1). Thus, electronic contributions to

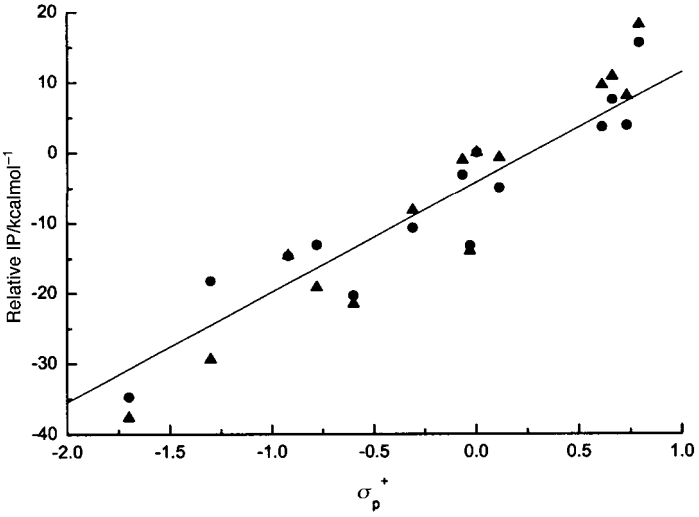


Figure 2. Correlation between relative IPs of catechols (●, $r = 0.96698$) and monophenols (▲, $r = 0.96207$) and σ_p^+.

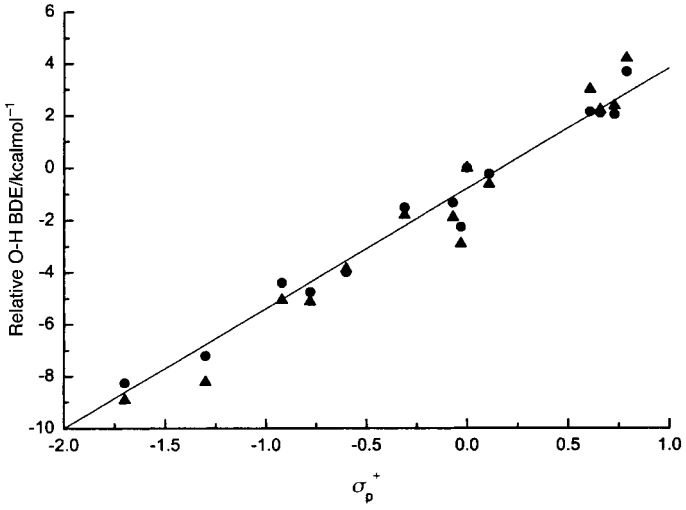


Figure 1. Correlation between relative O–H BDEs of catechols (●, $r = 0.98552$) and monophenols (▲, $r = 0.98028$) and σ_p^+.

O–H BDEs play a predominant role in the substituent effects. Similarly, the substituent effect on IPs of catechols is also near to the effect on IPs of monophenols (Table 1, Figure 2). This enables the catechol moiety to be an excellent lead structure and to take advantage of relatively low O–H BDE and relatively high IP in the rational design of antioxidants. For instance, the O–H BDE of OMe-substituted catechol is 14.76 (10.01 + 4.75) kcal mol^{-1} lower than that of phenol; however, its IP is only 23.39 (14.02 + 9.37) kcal mol^{-1} lower than that of phenol (Table 1). In contrast, even if 5-pyrimidinol or phenol were substituted by two *ortho* methyls and one *para*-NMe_2, the O–H BDEs being 13 (15.5 – 87.1 + 89.6) kcal mol^{-1} or 14.8 kcal mol^{-1} lower than those of phenol,[17] their IPs would be 28.4 (52.7 – 195.4 + 219.7) kcal mol^{-1} or 43.1 kcal mol^{-1} lower than those of phenol.[17] Apparently, substituted catechols will be much more stable to air oxidation than substituted monophenols, provided they have similar O–H BDEs. In addition, the second hydroxyl in methoxyl

catechol is also abstractable, with an O–H BDE as low as 71.04 kcal mol^{-1}. Hence, on the basis of methoxyl catechol, it is possible to design novel antioxidants with excellent properties, and their design is undertaken in our laboratory.[61]

Furthermore, since the electronic effects of substituents are composed of two main parts, a field/inductive component, represented by parameter F, and a resonance component, characterized by parameter R^+, that is, $\sigma_p^+ = F + R^+$,[60] it is interesting to determine whether the O–H BDEs of catechols are mainly governed by field/inductive effects or resonance effects? From correlation studies (Figures 3 and 4), it can be found that the correlation between O–H BDE and R^+ ($r = 0.96468$) is much better than that between O–H BDE and F ($r = 0.56828$); the correlation suggests that the O–H BDEs of catechols are mainly governed by the resonance effect. This is similar to the observation on O–H BDEs of *para*-substituted monophenols[39a] and will be helpful to elucidate the SAR for flavonoid antioxidants.

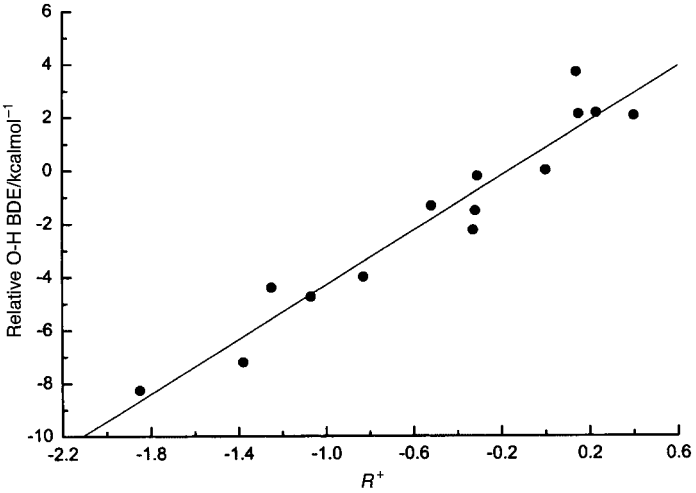


Figure 3. Correlation between relative O–H BDEs of catechols and R^+ ($r = 0.96468$).

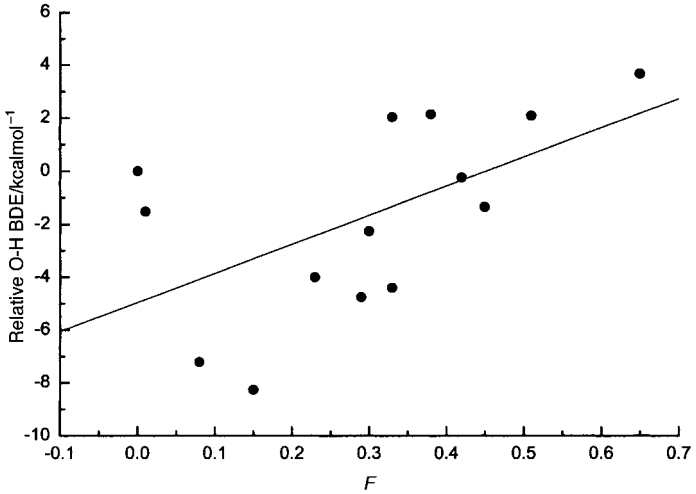
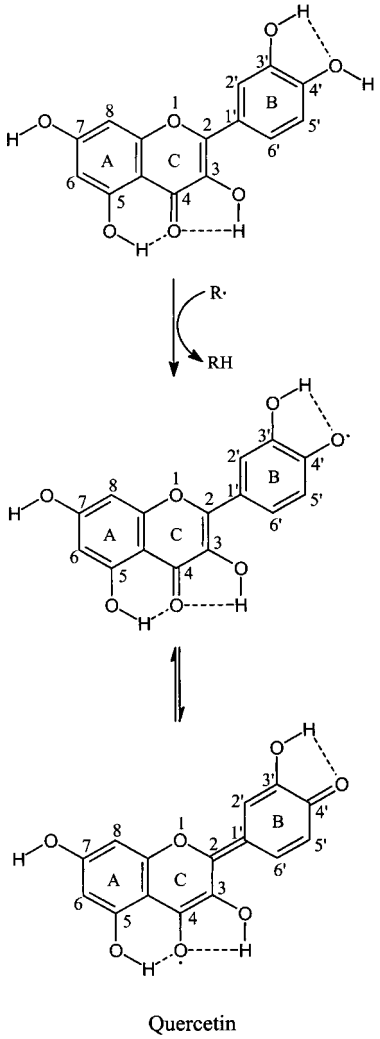


Figure 4. Correlation between relative O–H BDEs of catechols and F ($r = 0.56828$).

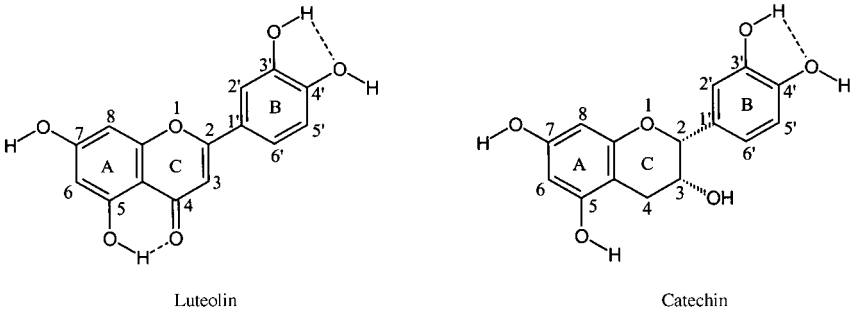
1,4-Pyrone effect on O–H BDEs of catechols and elucidation of structure – activity relationships for flavonoid antioxidants: Flavonoids have received considerable attention in recent years, owing to their excellent antioxidant and pharmacological activities.[23–30, 62–66] Two structural factors are considered to be particularly favorable to enhance the flavonoid antioxidant activity. First, a catechol moiety is necessary,[23–30, 65–67] which can be easily understood from the above discussions. Second, a 2,3-double bond in conjugation with the 4-oxo function in ring C, namely, a 1,4-pyrone moiety, is also helpful,[25, 27, 65–67] which was considered to stem from the high resonance between the rings A, B, and C (Scheme 5). In addition, through a quantum chemical calculation, van Acker et al.[68] indicated that the torsion angle between rings B and C was also important for the free radical scavenging activity of flavonoids. The smaller the angle, the better the resonance between rings B and C, the more stable the phenoxyl radical in ring B, and the more active the flavonoids. For instance, quercetin (Scheme 5) is more active than luteolin (Scheme 6), because the rings B and C of the former are more planar than those of the latter owing to the existence of the intramolecular hydrogen bond between 3-OH and 6′-H in the former.[68–70] However, the SAR was brought into question by experiments, which indicated that catechin is more active than luteolin,



Quercetin

Scheme 5.

0947-6539/03/0902-0506 $ 20.00+.50/0 *Chem. Eur. J.* **2003**, *9*, No. 2



Scheme 6.

though luteolin is better conjugated (Scheme 6).[25] DFT calculations suggested that the O–H BDE of catechin was indeed lower than that of luteolin.[39a] Apparently, to understand the SAR, we will have to investigate the 1,4-pyrone effect on the O–H BDE of catechol.

From the above discussion, it is clear that although the resonance effect is predominant in determining O–H BDEs of catechols, only the resonance effect of ED groups reduces the O–H BDEs, and resonance from EW groups has an opposite effect. Therefore, theoretically, the 1,4-pyrone moiety is not favorable for reducing the O–H BDE of catechol as a result of its EW property.

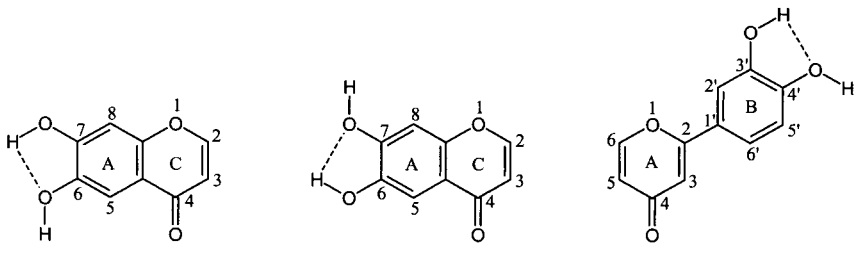
To quantitatively evaluate the 1,4-pyrone effect on O–H BDE of catechol, we designed two kinds of structures, catechol in ring A (**6** and **7**, Scheme 7) and catechol in ring B (**8**, Scheme 7), because both kinds of structures exist in flavonoids. The O–H BDEs for **6** or **7** indicate that the 1,4-pyrone raises the O–H BDE by 2.62 or 2.45 kcal mol^{-1} compared with that of catechol.[71] However, owing to the poor conjugation between 1,4-pyrone and catechol in ring B, 1,4-pyrone has little effect on the O–H BDE,[72] implying that flavonoids with catechol in ring B will be more active at scavenging free radicals than those with catechol in ring A; this has been observed by experiments.[28, 29]

In brief, although 1,4-pyrone extends the conjugation system of flavonoids, it is not beneficial for reducing the O–H BDE as a result of its electron-withdrawing property, and thus, it is unlikely to be favorable for enhancing the H-abstraction activity of flavonoids.

Conclusion

The catechol moiety has the advantages of relatively low O–H BDE, relatively high IP, and relatively low toxicity of the product generated in the radical scavenging process. In addition, the substituent effects on O–H BDEs and IPs for catechols are roughly the same as for monophenols, which gives catechol more potential than monophenol to be used as a lead compound in the rational design of antioxidants.

Similar to monophenols, the O–H BDEs of catechols are also mainly governed by the resonance effect of the substituents. However, only the resonance effect of ED groups reduces the O–H BDE, and the resonance from EW groups has an opposite effect. Accordingly, although 1,4-pyrone extends the conjugation system of flavonoids, it is not favorable for reducing the O–H BDE of the catechol in flavonoids as a result of its EW property. Hence, the SAR for flavonoids in the scavenging of free radicals was elucidated. The necessity of a catechol moiety was demonstrated, but the 1,4-pyrone effect was questioned.



Scheme 7.

Acknowledgements

This study was partially supported by the National Natural Science Foundation of China (Grant No. 30100035). We are grateful to Prof. Mark S. Gordon, Ames Laboratory, Iowa State University (USA), for his helpful suggestions.

[1] G. W. Burton, K. U. Ingold, *Acc. Chem. Res.* **1986**, *19*, 194–201.
[2] G. Scott, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 165–170.
[3] B. Halliwell, R. Aeschbach, J. Loliger, O. I. Aruoma, *Food Chem. Toxicol.* **1995**, *33*, 601–617.
[4] O. I. Aruoma, *Free Radical Biol. Med.* **1996**, *20*, 675–705.
[5] For reviews, see: a) *Handbook of Synthetic Antioxidants* (Eds.: L. Packer, E. Cadenas), Marcel Dekker, New York, **1997**, pp. 1–52; b) N. Noguchi, E. Niki, *Free Radical Biol. Med.* **2000**, *28*, 1538–1546; c) H. Y. Zhang, D. Z. Chen, *Acta Biophys. Sin.* **2000**, *16*, 1–9.
[6] As O–H BDE correlates well with the activation energy of the H-abstraction reaction,[7, 8] there exists a good linear relationship between O–H BDE and the logarithm of the radical scavenging rate constant for the phenolic antioxidants.[9–12] Thus, O–H BDE has been widely used to characterize the radical scavenging activity.[13–17]
[7] K. Tanaka, S. Sakai, S. Tomiyama, T. Nishiyama, F. Yamada, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2677–2680.
[8] S. Tomiyama, S. Sakai, T. Nishiyama, F. Yamada, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 299–304.
[9] S. A. B. E. van Acker, L. M. H. Koymans, A. Bast, *Free Radical Biol. Med.* **1993**, *15*, 311–328.
[10] E. Migliavacca, P. A. Carrupt, B. Testa, *Helv. Chim. Acta* **1997**, *80*, 1613–1626.
[11] a) H. Y. Zhang, *J. Am. Oil Chem. Soc.* **1998**, *75*, 1705–1709; b) H. Y. Zhang, Y. M. Sun, G. Q. Zhang, D. Z. Chen, *Quant. Struct.-Act. Relat.* **2000**, *19*, 375–379.
[12] M. C. Foti, E. R. Johnson, M. R. Vinqvist, J. S. Wright, L. R. C. Barclay, K. U. Ingold, *J. Org. Chem.* **2002**, *67*, 5190–5196.
[13] G. W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad, K. U. Ingold, *J. Am. Chem. Soc.* **1985**, *107*, 7053–7065.
[14] a) H. Y. Zhang, *J. Am. Oil. Chem. Soc.* **1999**, *76*, 745–748; b) H. Y. Zhang, N. Ge, Z. Y. Zhang, *Acta Pharmacol. Sin.* **1999**, *20*, 363–366; c) H. Y. Zhang, D. Z. Chen, *Acta Biochim. Biophys. Sin.* **2000**, *32*, 317–321; d) Y. M. Sun, X. L. Wang, H. Y. Zhang, D. Z. Chen, *Quant. Struct.-Act. Relat.* **2001**, *20*,

139 – 142; e) H. Y. Zhang, L. F. Wang, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 225 – 227; f) Y. M. Sun, H. Y. Zhang, D. Z. Chen, C. B. Liu, *Org. Lett.* **2002**, *4*, 2909 – 2911; g) H. Y. Zhang, L. F. Wang, *J. Am. Oil. Chem. Soc.* **2002**, *79*, 943 – 944.
[15] J. S. Wright, D. J. Carpenter, D. J. McKay, K. U. Ingold, *J. Am. Chem. Soc.* **1997**, *119*, 4245 – 4252.
[16] J. S. Wright, E. R. Johnson, G. A. DiLabio, *J. Am. Chem. Soc.* **2001**, *123*, 1173 – 1183.
[17] D. A. Pratt, G. A. DiLabio, G. Brigati, G. F. Pedulli, L. Valgimigli, *J. Am. Chem. Soc.* **2001**, *123*, 4625 – 4626.
[18] V. W. Bowry, K. U. Ingold, *Acc. Chem. Res.* **1999**, *32*, 27 – 34.
[19] A. Watanabe, N. Noguchi, A. Fujisawa, T. Kodama, K. Tamura, O. Cynshi, E. Niki, *J. Am. Chem. Soc.* **2000**, *122*, 5438 – 5442.
[20] N. Gotoh, N. Noguchi, J. Tsuchiya, K. Morita, H. Sakai, H. Shimasaki, E. Niki, *Free Radical Res.* **1996**, *24*, 123 – 134.
[21] N. Noguchi, Y. Okimoto, J. Tsuchiya, O. Cynshi, T. Kodama, E. Niki, *Arch. Biochem. Biophys.* **1997**, *347*, 141 – 147.
[22] N. Noguchi, Y. Iwaki, M. Takahashi, E. Komuro, Y. Kato, K. Tamura, O. Cynshi, T. Kodama, E. Niki, *Arch. Biochem. Biophys.* **1997**, *342*, 236 – 243.
[23] S. V. Jovanovic, S. Steenken, M. Tosic, B. Marjanovic, M. G. Simic, *J. Am. Chem. Soc.* **1994**, *116*, 4846 – 4851.
[24] S. V. Jovanovic, S. Steenken, Y. Hara, M. G. Simic, *J. Chem. Soc. Perkin Trans. 2* **1996**, *11*, 2497 – 2504.
[25] V. A. Roginsky, T. K. Barsukova, A. A. Remorova, W. Bors, *J. Am. Oil Chem. Soc.* **1996**, *73*, 777 – 786.
[26] M. Foti, M. Piattelli, M. T. Baratta, G. Ruberto, *J. Agric. Food. Chem.* **1996**, *44*, 497 – 501.
[27] C. A. Rice-Evans, N. J. Miller, G. Paganga, *Free Radical Biol. Med.* **1996**, *20*, 933 – 956.
[28] M. Ogata, M. Hoshi, K. Shimotohno, S. Urano, T. Endo, *J. Am. Oil Chem. Soc.* **1997**, *74*, 557 – 562.
[29] A. Arora, M. G. Nair, G. M. Strasburg, *Free Radical Biol. Med.* **1998**, *24*, 1355 – 1363.
[30] P.-G. Pietta, *J. Nat. Prod.* **2000**, *63*, 1035 – 1042.
[31] There have been many efforts devoted to determining O–H BDE experimentally or theoretically. For recent reviews, see: a) R. M. Borges dos Santos, J. A. Martinho Simoes, *J. Phys. Chem. Ref. Data* **1998**, *27*, 707 – 739; b) *Handbook of Antioxidants*, 2nd ed., (Eds.: E. T. Denisov, T. G. Denisova), CRC, Florida, **2000**.
[32] a) M. Lucarini, P. Pedrielli, G. F. Pedulli, *J. Org. Chem.* **1996**, *61*, 9259 – 9263; b) G. Brigati, M. Lucarini, V. Mugnaini, G. F. Pedulli, *J. Org. Chem.* **2002**, *67*, 4828 – 4832.
[33] H. Y. Zhang, D. Z. Chen, *Chin. J. Org. Chem.* **2001**, *21*, 66 – 70.
[34] Y. D. Wu, D. K. W. Lai, *J. Org. Chem.* **1996**, *61*, 7904 – 7910.
[35] T. Brinck, M. Haeberline, M. Jonsson, *J. Am. Chem. Soc.* **1997**, *119*, 4239 – 4244.
[36] M. I. de Heer, H.-G. Korth, P. Mulder, *J. Org. Chem.* **1999**, *64*, 6969 – 6975.
[37] G. A. DiLabio, D. A. Pratt, A. D. LoFaro, J. S. Wright, *J. Phys. Chem. A* **1999**, *103*, 1653 – 1661.
[38] T. Brinck, H.-N. Lee, M. Jonsson, *J. Phys. Chem. A* **1999**, *103*, 7094 – 7104.
[39] a) H. Y. Zhang, Y. M. Sun, D. Z. Chen, *Quant. Struct.-Act. Relat.* **2001**, *20*, 148 – 152; b) H. Y. Zhang, Y. M. Sun, X. L. Wang, *J. Org. Chem.* **2002**, *67*, 2709 – 2712.
[40] Y. M. Sun, H. Y. Zhang, D. Z. Chen, *Chin. J. Chem.* **2001**, *19*, 657 – 661.
[41] a) G. A. DiLabio, D. A. Pratt, J. S. Wright, *Chem. Phys. Lett.* **1999**, *311*, 215 – 220; b) G. A. DiLabio, D. A. Pratt, J. S. Wright, *J. Org. Chem.* **2000**, *65*, 2195 – 2203.
[42] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785 – 789.
[43] P. J. Stevenes, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623 – 11627.
[44] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372 – 1377.
[45] J. J. Gajewski, K. E. Gilbert, J. McKelvey, *Adv. Mol. Model.* **1990**, *2*, 65 – 92.
[46] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902 – 3909.
[47] A. P. Scott, L. Radom, *J. Phys. Chem.* **1996**, *100*, 16502 – 16513..
[48] Gaussian 94 (Revision E.3), M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1995**.
[49] DFT calculations with other basis sets provided evidence of similar *ortho*-hydroxyl effects, that is, -9.2 kcal mol^{-1},[16] -9.7 kcal mol^{-1},[50] and -10.0 kcal mol^{-1}.[12]
[50] F. Hino, L. A. Eriksson, M. R. A. Blomberg, P. E. M. Siegbahn, *Int. J. Quantum Chem.* **2000**, *76*, 714 – 723.
[51] M. Lucarini, V. Mugnaini, G. F. Pedulli, *J. Org. Chem.* **2002**, *67*, 928 – 931.
[52] L. R. C. Barclay, C. E. Edwards, M. R. Vinqvist, *J. Am. Chem. Soc.* **1999**, *121*, 6226 – 6231.
[53] M. Lucarini, G. F. Pedulli, M. Cipollone, *J. Org. Chem.* **1994**, *59*, 5063 – 5070.
[54] I. Vedernikova, E. Proynov, D. Salahub, A. Haemers, *Int. J. Quantum Chem.* **2000**, *77*, 161 – 173.
[55] Hino et al. also indicated that the IHB in the catechol radical was 5.3 kcal mol^{-1} stronger than that in the parent catechol.[50]
[56] M. M. Suryan, S. A. Kafafi, S. E. Stein, *J. Am. Chem. Soc.* **1989**, *111*, 1423 – 1429. Suryan et al. indicated that the IHB enthalpy of the catecholic radical would be at least 4.7 kcal mol^{-1} higher than that of *ortho*-methoxyl phenol. That is, the IHB enthalpy for the catechol radical should be higher than 9.1 (4.7 + 4.4) kcal mol^{-1}.
[57] A. S. Pannala, T. S. Chan, P. J. O'Brien, C. A. Rice-Evans, *Biochem. Biophys. Res. Commun.* **2001**, *282*, 1161 – 1168.
[58] Theoretically, the IP of α-T is 36.1 kcal mol^{-1} lower than that of phenol.[17]
[59] The Brown parameter is commonly used to characterize substituent electronic effects, especially for substituents conjugated with a reaction center which could effectively delocalize a positive charge.[60]
[60] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165 – 195.
[61] Following submission of the present paper, a very important publication appeared describing rationally designed phenolic antioxidants and naphthalene diols containing IHBs.[12] Thus, our prediction has been partially verified.
[62] C. Kandaswami, Jr., E. Middleton in *Free Radicals in Diagnostic Medicine* (Ed.: D. Armstrong), Plenum Press, New York, **1994**, pp. 351 – 448.
[63] C. Kandaswami, Jr., E. Middleton in *Natural Antioxidants*: *Chemistry, Health Effects, and Applications* (Ed.: F. Shahidi), AOCS, Champaign, **1996**, pp. 174 – 203.
[64] W. Bors, W. Heller, C. Michel, K. Stettmaier in *Handbook of Antioxidants* (Eds.: E. Cadenas, L. Packer), Marcel Dekker, New York, **1996**, pp. 409 – 466.
[65] W. Bors, C. Michel, *Biofactors* **1997**, *6*, 399 – 402.
[66] K. D. Croft, *Ann. N.Y. Acad. Sci.* **1998**, *854*, 435 – 442.
[67] W. Bors, W. Hetter, C. Michel, M. Saran, *Methods Enzymol.* **1990**, *186*, 343 – 355.
[68] S. A. B. E. van Acker, M. J. de Groot, D.-J. van den Berg, M. N. J. L. Tromp, G. D.-O. den Kelder, W. J. F. van der Vijgh, A. Bast, *Chem. Res. Toxicol.* **1996**, *9*, 1305 – 1312.
[69] On the contrary, recent ab initio calculations on flavonoids with HF/6-31G(d) methods indicated that the torsion angles between rings B and C were in the order of 20 – 30°, regardless of the presence of a OH group at C3. In fact, quercetin deviated greatly from coplanarity in solution.[70]
[70] M. Meyer, *Int. J. Quantum Chem.* **2000**, *76*, 724 – 732.
[71] The O–H BDEs of **6** (6-OH) and **7** (7-OH) were calculated to be 75.44 and 75.27 kcal mol^{-1}, respectively.
[72] The relative O–H BDEs for two conformations of **8** (4′-OH), planar and twisted, were calculated. The conformation for the radical is planar as a result of the resonance between rings A and B. However, the natural conformation for parent **8** is twisted ($\approx 8°$) as a result of the steric effect between rings A and B. Hence, the O–H BDE for planar **8** (72.75 kcal mol^{-1}) is a little lower than that for twisted **8** (73.25 kcal mol^{-1}). The difference between the two O–H BDEs, 0.5 kcal mol^{-1}, reflects the steric effect between rings A and B of the parent **8**.

Received: April 9, 2002
Revised: August 9, 2002 [F4007]

  0947-6539/03/0902-0508 $ 20.00+.50/0