

A Critical Evaluation of the Factors Determining the Effect of Intramolecular Hydrogen Bonding on the O–H Bond Dissociation Enthalpy of Catechol and of Flavonoid Antioxidants

Marco Lucarini,^{*,[a]} Gian Franco Pedulli,^{*,[a]} and Maurizio Guerra^{*,[b]}

Abstract: New experimental results on the determination of the bond dissociation enthalpy (BDE) value of 3,5-di-*tert*-butylcatechol, a model compound for flavonoid antioxidants, by the EPR radical equilibration technique are reported. By measurement of the equilibrium constant for the reaction between 3,5-di-*tert*-butylcatechol and the 2,6-di-*tert*-butyl-4-methylphenoxy radical, in UV irradiated isooctane solutions at different temperatures, it has been shown that the thermodynamic parameters for this reaction are $\Delta H^\circ = -2.8 \pm 0.1 \text{ kcal mol}^{-1}$ and $\Delta S^\circ = +1.3 \pm 0.2 \text{ cal mol}^{-1} \text{ K}^{-1}$. This demonstrates that the entropic variations in the hydrogen exchange reaction be-

tween phenols and the corresponding phenoxy radicals are also negligible when one of the reacting species is a polyphenol and that the EPR radical equilibration technique also allows the determination of the O–H BDEs in intramolecularly hydrogen-bonded polyphenols.

The BDE of 3,5-di-*tert*-butylcatechol ($78.2 \text{ kcal mol}^{-1}$) was determined to be identical to that of α -tocopherol. Through use of the group additivity rule, this piece of data was also used to

calculate the strength of the intramolecular hydrogen bond between the hydroxyl proton and the oxygen radical centre in the corresponding semiquinone radical ($5.6 \text{ kcal mol}^{-1}$), which is responsible both for the excellent antioxidant properties of catechols and for the BDE of catechol ($81.8 \text{ kcal mol}^{-1}$). These values are in poor agreement with those predicted by DFT calculations reported in the literature ($9.5 \text{ kcal mol}^{-1}$ and $77.6 \text{ kcal mol}^{-1}$, respectively). Extensive theoretical calculations indicate that the BDE of catechol is reproduced well ($81.6 \text{ kcal mol}^{-1}$) by use of diffuse functions on oxygen and the CCSD method.

Keywords: ab initio calculations • antioxidants • EPR spectroscopy • flavonoids • radicals

Introduction

The large interest in the bioactivity of the flavonoids of higher plants is at least in part due to the potential health benefits of these polyphenolic components.^[1] Their activity derives from their capability to inhibit the oxidative degradation of membranes by scavenging the peroxy radicals of phospholipids responsible for propagating the autoxidation

reaction. Free radical scavenging takes place through transfer of the hydroxylic hydrogen of phenols to the peroxy oxygen atom, and one of the factors characterising effective antioxidant behaviour in phenols is therefore a low value of the O–H bond dissociation enthalpy (BDE) since this facilitates the H-atom transfer.

In a recent paper^[2] we reported the determination, by the EPR radical equilibration technique,^[3] of the O–H BDE of 3,5-di-*tert*-butylcatechol (**1A**) and propyl gallate, which represent model compounds for flavonoid antioxidants. The BDE value of **1A** was obtained by measuring the room-temperature equilibrium constant for its reaction, in a benzene/di-*tert*-butyl peroxide mixture (9:1 v/v), with the phenoxy radical from 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 1), under the assumption that the entropic term can be neglected [Eq. (1)].

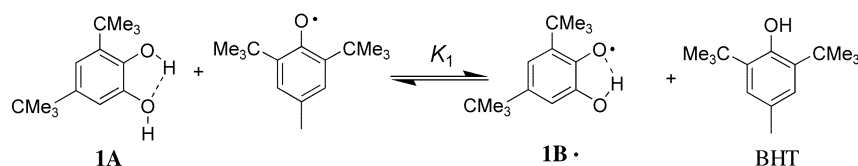
$$\text{BDE}(\mathbf{1A}) \cong \text{BDE}(\text{BHT}) - RT \ln(K_1) \quad (1)$$

The measured O–H bond strength of **1A** ($79.3 \pm 0.3 \text{ kcal mol}^{-1}$) was found to be much lower than the value calculated by the group additivity rule ($83.7 \text{ kcal mol}^{-1}$) with the

[a] Prof. M. Lucarini, Prof. G. F. Pedulli
Dipartimento di Chimica Organica "A. Mangini"
Università di Bologna, Via S. Donato 15
40127 Bologna (Italy)
Fax: (+39) 51244064
E-mail: lucarini@alma.unibo.it
pedulli@alma.unibo.it

[b] Dr. M. Guerra
I.S.O.F., Consiglio Nazionale delle Ricerche
Via P. Gobetti 101, 40129 Bologna (Italy)
E-mail: guerra@isof.cnr.it

Supporting information for this article is available on the WWW under <http://www.chemurj.org/> or from the author. It includes total energies and optimised geometries of the investigated species obtained at the highest level of theory.



Scheme 1. Equilibration between **1A** and the phenoxyl radical from 2,6-di-*tert*-butyl-4-methylphenol (BHT).

contributions of the various substituents being those obtained from monophenols.^[4] The difference between the calculated and the experimentally determined BDE values ($4.4 \text{ kcal mol}^{-1}$), much larger than the average deviation ($\pm 0.3 \text{ kcal mol}^{-1}$) between predicted and measured BDE values in monophenols,^[3,4] was attributed to the stabilisation of the semiquinone radical (**1B**·) from 3,5-di-*tert*-butylcatechol through the formation of an intramolecular hydrogen bond between the residual O–H group and the oxygen radical centre (Scheme 1). Since the H-bond strength in the unsubstituted catechol (**2A**) has been estimated to be $4.0 \text{ kcal mol}^{-1}$,^[5] it can be deduced that in the semiquinone radical **1B**· the O–H BDE value should be only slightly larger than in the parent catechol. The group additivity rule can also be used to calculate the BDE value of catechol (**2A**) as $82.9 \text{ kcal mol}^{-1}$, if it is recalled that the contributions due to the two *tert*-butyl groups in the 3- and 5-positions to the BDE of **1A** are -1.7 and $-1.9 \text{ kcal mol}^{-1}$,^[4a] respectively. Therefore, the *ortho*-hydroxyl effect with respect to phenol ($87.6 \text{ kcal mol}^{-1}$) turns out to be $-4.7 \text{ kcal mol}^{-1}$.

In contrast with this result, Zhang et al.^[6] have recently reported a density functional theory (DFT) study of the BDEs of catechol and related compounds, predicting an *ortho*-hydroxyl effect of $10.0 \text{ kcal mol}^{-1}$; that is, about twice as large as that found experimentally by the EPR radical equilibration technique.^[2] Thus, on the basis of these compu-

tational results, catechol, the O–H BDE value of which is calculated to be very close to that of α -tocopherol (α -TOH) ($78.2 \text{ kcal mol}^{-1}$),^[2] should show antioxidant properties almost as good as those of α -tocopherol, while the larger value estimated by EPR ($82.9 \text{ kcal mol}^{-1}$) implies a worse radical-scavenging ability. Zhang et al.^[6] emphasize the fact that their estimate is in agreement with previous ones obtained by the same DFT computational technique,^[7] and that 3,5-di-*tert*-butylcatechol is three times better than α -TOH at scavenging DPPH radicals in non-polar solvents,^[8] a result more consistent with their estimate of the BDE values of catechols. They therefore conclude that, because of the complexity of the H-atom abstraction reaction, the EPR equilibration technique is not appropriate for determination of the O–H BDEs in intramolecularly hydrogen-bonded polyphenols, although the method may still be applicable to monophenols or polyphenols without intramolecular hydrogen bonding, such as hydroquinones.

Herein we report new experimental and theoretical results that definitively demonstrate that the EPR equilibration technique also allows the determination of the O–H BDEs in intramolecularly hydrogen-bonded polyphenols.

Results and Discussion

The reasons given by Zhang et al. for judging the EPR equilibration technique inappropriate are that this method relies on the following two assumptions: i) the H-abstraction from 3,5-di-*tert*-butylcatechol to give **1B**· is regarded as a one-step reaction while probably being a two-step reaction as shown in Figure 1, and ii) the entropy change for the equilibration reaction is neglected.

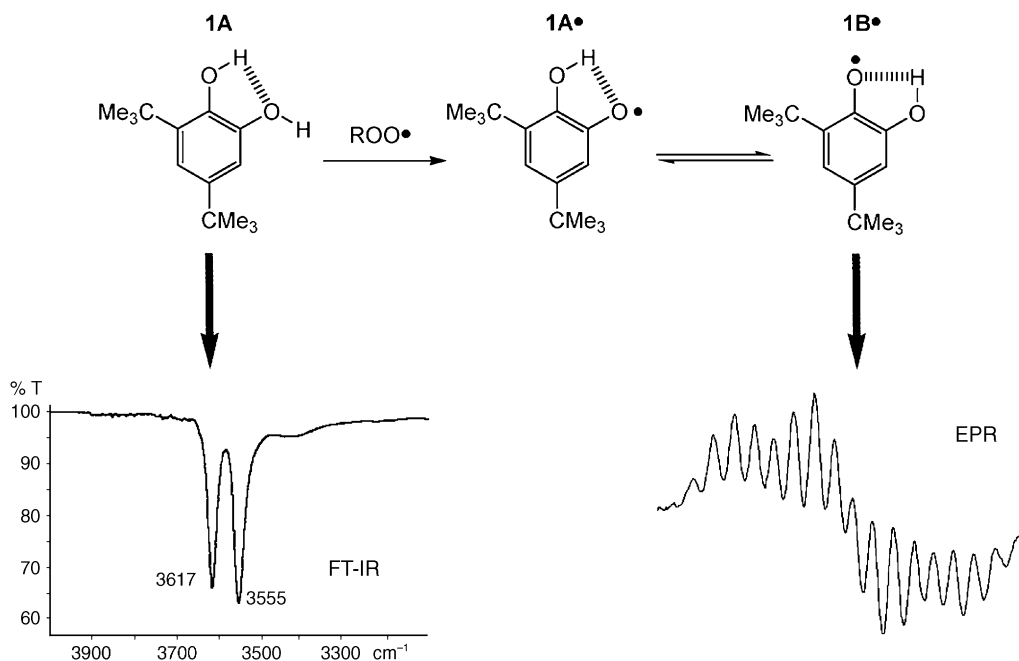


Figure 1. Vibrational spectrum of 3,5-di-*tert*-butylcatechol (**1A**) in the 3100–4000 cm^{-1} region and EPR spectrum of the corresponding semiquinone radical (**1B**·).

The first point is hardly understandable, since thermodynamics requires that the free energy difference between two states is independent of the reaction pathway, being the same no matter how complex the overall reaction. The only problem might concern the identification of the initial and final states of the reaction. In the case of 3,5-di-*tert*-butylcatechol the structure of the initial state (**1A** in Figure 1), in CCl_4 solution at the same concentration (0.1 M) as used in the EPR equilibration studies, was determined by FT-IR spectroscopy (see Figure 1), which showed two sharp peaks of similar intensity centred at 3617 cm^{-1} , characteristic of a free OH group in position 1, and at 3555 cm^{-1} due to the intramolecularly H-bonded OH in position 2. The final state, on the other hand, was unambiguously identified on the basis of the EPR spectral parameters ($a(1\text{H}_{\text{ring}}) = 1.74\text{ G}$, $a(1\text{H}_{\text{ring}}) = 0.31\text{ G}$, $a(1\text{H}_{\text{OH}}) = 1.45\text{ G}$, $a(9\text{H}_{\text{Bu}}) = 0.39\text{ G}$, $g = 2.0044$), consistent with structure **1B**.^[2]

The formation of the other possible species **1A**·, with the radical centred on the oxygen in position 1, can be discounted since larger splittings (ca. 10 and 5 G from the protons at positions 4 and 6, respectively) would be expected in this case. Of course, we can not exclude the possibility that this species is initially formed, since it would immediately rearrange to the observed thermodynamically more stable radical.^[9]

As far as the second point is concerned, the neglecting of the entropy of reaction in the specific case of catechol **1A** was an extrapolation based on previous experiments showing that the entropy of a hydrogen exchange reaction for several pairs of monophenols is negligible.^[3] In addition, the equilibration reaction in benzene between 2,4,6-trimethylphenol and a bisphenol in which both hydroxyl hydrogens are intramolecularly hydrogen bonded was found to be characterised by a negligible entropy variation.^[10] On the other hand, a large ΔS would only be expected for the reaction shown in Scheme 1 if intramolecular hydrogen bond formation were associated with a large entropy change. As early as the 1950s, it had instead been shown that this is not the case in *ortho*-substituted phenols,^[11] and additional evidence was also recently reported by Mulder and co-workers.^[4b] The reason for this behaviour is that the contribution of the O–H vibration to the overall entropy is already negligible in a free hydroxyl group.

However, to confirm on an experimental basis that the entropy variation associated with the H atom transfer reaction shown in Scheme 1 can safely be neglected, we carried out a very careful study of the temperature dependence of the equilibrium constant K_1 . Initially, the equilibrium was studied in the 296–383 K temperature range in a toluene/*di-tert*-butyl peroxide (9:1 v/v) solution. From these measurements the van't Hoff plot shown in Figure 2 was obtained, providing $\Delta H^\circ = -0.2 \pm 0.2\text{ kcal mol}^{-1}$ and $\Delta S^\circ = +5.0 \pm 0.6\text{ cal mol}^{-1}\text{ K}^{-1}$. These values unexpectedly indicate that the entropic contribution to the hydrogen atom exchange reaction is significantly positive and that the enthalpic term is close to zero, which implies that some interaction with a favourable enthalpy and a negative entropy is lost on passing from left to right in the reaction shown in Scheme 1. This result is opposite to what would be expected (vide infra) on

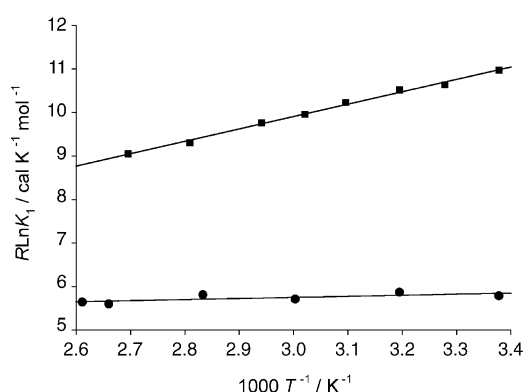


Figure 2. Experimentally determined van't Hoff plot for the equilibrium shown in Scheme 1 in a toluene/*di-tert*-butyl peroxide (9:1 v/v) solution (full circles) and in isooctane (full squares).

the basis of the results reported in reference [6], and is hard to interpret without admitting the intervention of solvent molecule in the reaction.

Actually, catechols have been found to experience strong kinetic solvent effects in hydrogen atom abstraction by nitrogen- and oxygen-centred radicals.^[8] Moreover, by measuring the equilibrium constant for the reaction shown in Scheme 1 in a hydrogen-bond-accepting (HBA) solvent such as *tert*-butyl alcohol we found an O–H BDE value for **1A** 1.4 kcal mol^{-1} larger than that determined in the benzene/*di-tert*-butyl peroxide (9:1) mixture.^[2] Thus, the substituted catechol behaves similarly to other phenolic antioxidants in which hydrogen bonding by HBA solvents induces an increase in the BDE value, through preferential stabilisation of the starting phenol rather than of the phenoxyl radical.^[12] These determinations were carried out under the assumption that the O–H bond energy of BHT in Me_2COH is the same as in hydrocarbons, due to the steric protection of the hydroxyl group by the *ortho tert*-butyl substituents in BHT, which prevents its solvation by HBA solvents.^[13]

Thus, the van't Hoff plot shown in Figure 2 seems to suggest that the experiments performed in benzene containing some *di-tert*-butyl peroxide as radical photoinitiator are also somewhat affected by solute–solvent interactions. It should be pointed out that our previous determinations of BDE values of phenolic antioxidants were carried out in benzene ($\beta_2^{\text{H}} = 0.14$), as many autoxidation experiments are usually performed in styrene, which is characterised by a similar β_2^{H} value (0.18).^[14]

To determine the contributions of both benzene and peroxide to the solvent effect we studied the equilibrium shown in Scheme 1 in pure isooctane, pure benzene and pure *di-tert*-butyl peroxide. EPR radical equilibration experiments (Figure 3) carried out at room temperature provided the equilibrium constants at 296 K as 250 in isooctane, as 51 in benzene, and as 6.3 in pure *di-tert*-butyl peroxide.

Ingold and co-workers have recently proposed an empirical equation, which quantifies the kinetic solvent effect at room temperature.^[15] The equation can be expressed as: $\log K_1^{\text{S}} = \log K_1^0 - 8.3\alpha_2^{\text{H}}\beta_2^{\text{H}}$, where K_1^0 refers to the equilibrium constant in a non-HBA solvent for which $\beta_2^{\text{H}} = 0$, such as isooctane, and K_1^{S} is the corresponding equilibrium con-

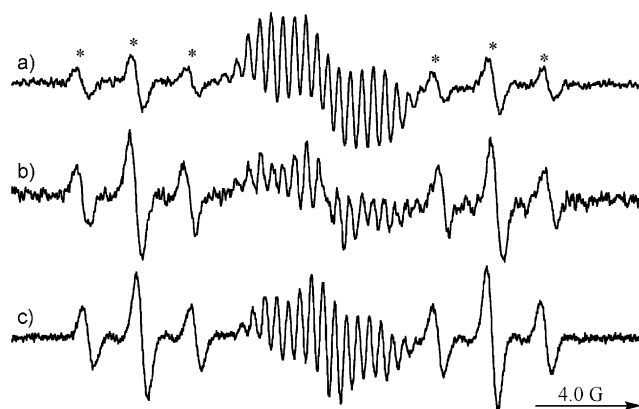


Figure 3. EPR spectra (296 K) obtained by photolysis of BHT/**1A** mixtures in isooctane (a, [BHT]/[**1A**] = 21.3), benzene (b, [BHT]/[**1A**] = 21.3) and di-*tert*-butyl peroxide (c, BHT/[**1A**] = 2.90).

stant in the HBA solvent S. By using $\beta_2^H = 0.14$ for benzene, $\beta_2^H = 0.33$ for di-*tert*-butyl peroxide^[16] and $\alpha_2^H = 0.62$ for the catechol^[17] we obtained $K_1^{\text{Benzene}} = 48$ and $K_1^{\text{Peroxide}} = 5$, in very good agreement with the experimentally ascertained EPR values (51 and 6.3, respectively). This result implies that, with phenols characterised by high hydrogen bond donor (HBD) abilities, the presence of some peroxide in the solution can also significantly influence the results. On the other hand, with phenols bearing electron-donating substituents, such as α -tocopherol, characterised by a weaker hydrogen bond donating ability, the presence of a small amount of peroxide in the reaction mixture does not significantly affect the EPR equilibration measurements.^[3]

On the basis of the above considerations and in order to avoid any effect due to solute–solvent interactions, the temperature dependence of the equilibrium constant for the reaction shown in Scheme 1 was investigated in isooctane solutions devoid even of trace amounts of peroxide. When these solutions, previously deoxygenated by bubbling nitrogen, were irradiated, reasonably intense EPR signals were observed. Analysis of the van't Hoff plot (see Figure 2) provided the following thermodynamic parameters: $\Delta H^\circ = -2.8 \pm 0.1 \text{ kcal mol}^{-1}$ and $\Delta S^\circ = +1.3 \pm 0.2 \text{ cal mol}^{-1} \text{ K}^{-1}$. Since the O–H BDE value of the reference phenol BHT is $81.0 \text{ kcal mol}^{-1}$, this means that the BDE of 3,5-di-*tert*-butylcatechol (**1A**) is $78.2 \text{ kcal mol}^{-1}$; that is, identical to that of α -tocopherol. Through subtraction of the contributions due to the 3- and 5-*tert*-butyl groups, the BDE of catechol **2A** is calculated as $81.8 \text{ kcal mol}^{-1}$ and the *ortho* hydroxyl effect will thus be $-5.8 \text{ kcal mol}^{-1}$; that is, $4.2 \text{ kcal mol}^{-1}$ lower than that computed by Zhang and co-workers.^[6]

To validate the large difference between these experimental results and those reported in reference [6], the ΔH° and ΔS° values for the reaction shown in Scheme 1 were estimated by assuming the *ortho*-hydroxyl effect of $10.0 \text{ kcal mol}^{-1}$ given by Zhang et al.^[6] and a ΔG° value of the reaction equal to the value measured by EPR spectroscopy ($-3.2 \text{ kcal mol}^{-1}$) at 296 K. The calculated values ($\Delta H^\circ = -7.0 \text{ kcal mol}^{-1}$ and $\Delta S^\circ = -12.8 \text{ kcal mol}^{-1}$)^[18] indicate that Zhang's parameters would predict a largely negative reac-

tion entropy, in disagreement with these experimental results.

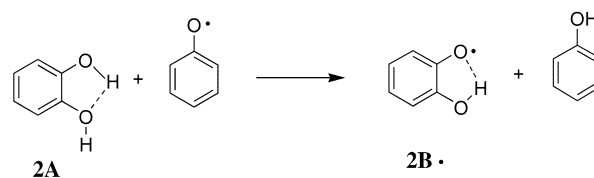
The above data can also be used to calculate the strength of the intramolecular hydrogen bond between the hydroxyl proton and the oxygen radical centre in the semiquinone radical **1B**. By use of the group additivity rule again and by considering the contribution of an *ortho*-hydroxyl group to be identical to that of an *ortho*-methoxy substituent (-0.2),^[4a] the predicted BDE value is computed to be $5.6 \text{ kcal mol}^{-1}$ higher than the experimentally measured value of $78.2 \text{ kcal mol}^{-1}$. This difference can be attributed to the formation of the intramolecular hydrogen bond in radical **1B** and therefore represents the strength of this H-bond. This is larger than the corresponding H-bond strength (ca. $4.0 \text{ kcal mol}^{-1}$)^[5] in the parent catechol, by about $1.6 \text{ kcal mol}^{-1}$. The intramolecular H-bond in the semiquinone radical **1B** is therefore much weaker than predicted by the DFT calculations reported in the literature (ca. $8\text{--}9.5 \text{ kcal mol}^{-1}$).^[6,7]

Recently, we have shown that the BDEs of *para*-substituted phenols (ArOH) are predicted very well by the DFT method at the simple B3LYP6–31G* level in conjunction with the isodesmic approach by use of Equation 2.

$$\text{BDE}(\text{ArOH}) = \text{BDE}_{\text{exp}}(\text{PhOH}) + [E_{\text{calcd}}(\text{ArO}^\bullet) - E_{\text{calcd}}(\text{ArOH})] - [(E_{\text{calcd}}(\text{PhO}^\bullet) - E_{\text{calcd}}(\text{PhOH}))] \quad (2)$$

Estimation of zero point vibrational energy (ZPVE), thermal correction to the enthalpy and enlargement of the basis set (6–311++G**) were found to have negligible effect.^[19]

The BDE of catechol **2A** (Scheme 2) is computed by the isodesmic approach to be $77.0 \text{ kcal mol}^{-1}$ at the simple B3LYP/6–31G* level; that is, an *ortho*-hydroxyl effect



Scheme 2. Bond dissociation of catechol **2A**.

($10.6 \text{ kcal mol}^{-1}$) comparable to that computed at the B3LYP/6–31G** level by Zhang et al.^[6] as would be expected since Equation (2) provides relative BDEs with respect to phenol (PhOH). In Scheme 2 the total number and types of bonds is conserved, so there should be cancellation of errors due mainly to electron correlation on the two sides of the reaction. Thus, the large difference between the *ortho*-hydroxyl effect ($-10.0 \text{ kcal mol}^{-1}$) on the BDE of catechol computed at the B3LYP/6–31G** level and that determined by the EPR radical equilibration technique ($-5.8 \text{ kcal mol}^{-1}$) is surprising.

Calculations were then performed on the substituted catechol **1** in order to compare theory and experiment directly. B3LYP/6–31G* calculations predict the semiquinone radical

1A• to be considerably less stable than **1B**• (by 2.4 kcal mol⁻¹ including the ZPVE correction of 0.1 kcal mol⁻¹), with a relatively low barrier to isomerisation (4.9 kcal mol⁻¹ including the ZPVE correction of 2.3 kcal mol⁻¹), in agreement with the ESR evidence. The BDE of **1A** is computed to be 73.5 kcal mol⁻¹ by the isodesmic approach and without the ZPVE correction; that is, the two *tert*-butyl groups reduce the BDE of catechol by 3.5 kcal mol⁻¹, in excellent agreement with the value estimated from the group additivity rule (3.6 kcal mol⁻¹). This suggests that the simple B3LYP/6–31G* level, in conjunction with the isodesmic approach, predicts the effects on the BDE due to electronic perturbations very well, but is inadequate to describe correctly the intramolecular H-bonding present in catechol but absent in phenol. Subsequently, the effects of vibrations and basis set on the BDE of the unsubstituted catechol **2A** were investigated by the DFT-B3LYP method. Interestingly, the ZPVE correction cannot be neglected as in *para*-substituted phenols, being as large as 0.9 kcal mol⁻¹. Furthermore, Table 1

Table 1. O–H BDE for catechol **2A** computed at different levels of theory by the isodesmic approach [Eq. (2)]. The H-bond interaction (HBI) in catechol **2A** and in the parent semiquinone radical **2B**•; together with the *ortho*-OH effect in **2C**^[a], are also reported.^[b]

Method	BDE	HBI in 2A	HBI in 2B •	<i>o</i> -OH effect on BDE 2A/2C
B3LYP/6–31G*	77.9	4.2	9.5	–0.2
B3LYP/6–31G**	77.9	4.2	9.4	–0.3
B3LYP/6–31+G*	79.3	4.3	8.8	0.4
B3LYP/6–31++G**	79.3	4.3	8.7	0.4
B3LYP/6–311++G**	79.2	4.3	8.6	0.3
CCSD/6–31G*	80.6	4.6	8.3	0.8
CCSD/6–31+G*	81.6	4.7	8.0	1.9
CCSD/6–31++G**	81.5	4.7	7.9	1.8
exp	81.8		5.6 ^[c]	

[a] The *ortho*-OH contribution to BDE without the HB interaction in the semiquinone radical (**2C**•). [b] Energy values (kcal mol⁻¹) include the ZPVE correction estimated at the B3LYP/6–31G* level. [c] Estimated by the group additivity rule.

shows that addition of diffuse functions on oxygen (6–31+G*) sizeably increases (1.4 kcal mol⁻¹) the BDE of catechol. Addition of polarisation functions and diffuse functions on hydrogen (6–31++G**) as well as enlargement of the basis set from the valence double ζ (6–31++G**) to the valence triple ζ (6–311++G**) basis set has little effect. It should be noted that the barrier to the **1A**•→**1B**• isomerisation decreases significantly on going from the 6–31G* (4.9 kcal mol⁻¹) to the 6–31++G** (3.8 kcal mol⁻¹) basis set. This value is slightly higher than the barrier (2.8 kcal mol⁻¹) to isomerisation between the two equivalent sites in the 3,6-di-*tert*-butyl semiquinone radical determined experimentally by ESR spectroscopy.^[20] As expected, the relative stability is much less affected by the enlargement of the basis set, being computed to be 2.2 kcal mol⁻¹ at the B3LYP/6–31++G** level.

Anyway, the BDE of catechol **2A** remains significantly underestimated with respect to the experimentally measured value, by about 2 kcal mol⁻¹ with use of the B3LYP method and moderately large basis sets. The BDE of catechol was therefore also estimated by the more reliable coupled cluster method with single and double excitations (CCSD). The BDE values reported in Table 1 confirm that addition of polarisation and diffuse functions on hydrogen also has negligible effect on the BDE values when an ab initio method including electron correlation is used. Importantly, the BDE of catechol increases by about 2 kcal mol⁻¹ on going from the B3LYP to the CCSD method, so that agreement between theory and experiment becomes excellent.

The H–bond interaction in catechol **2A** and in semiquinone radical **2B**• were then estimated by also carrying out calculations on the less stable conformers **2C** and **2C**•, where the H–bond interaction is absent.

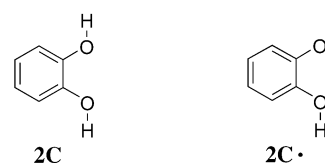


Table 1 shows that the HB interaction in catechol **2A** depends little on the basis set and increases slightly (by about 0.5 kcal mol⁻¹) on going from the DFT method to the correlated CCSD method. Its value (about 4.5 kcal) is in accord with previous estimates. The ZPVE correction is negligible, being computed as 0.01 kcal mol⁻¹ at the B3LYP/6–31G* level. On the other hand, the HB interaction in the semiquinone radical **2B**• depends on the theoretical method and is significantly affected by addition of diffuse functions on heavy atoms. Interestingly, the ZPVE correction is computed to be considerable (–0.52 kcal mol⁻¹). The decrease of 1.6 kcal mol⁻¹ on going from the B3LYP/6–31G** to the CCSD/6–31++G** level accounts for about 40% of the discrepancy between the experimentally determined value and previous theoretical DFT calculations. However, the best theoretical value (7.9 kcal mol⁻¹ at the CCSD/6–31++G** level) is 2.3 kcal mol⁻¹ higher than the value determined by the group additivity rule (5.6 kcal mol⁻¹). Since the experimental BDE value of **2A** is reproduced well by CCSD/6–31++G** calculations in conjunction with the isodesmic approach, the discrepancy between experiment and theory in the HBI value in the semiquinone **2B**• could be due to a different estimate of the *o*-OH effect. Indeed, Table 1 shows that the value of –0.2 kcal mol⁻¹ is about 2 kcal lower than that estimated at the CCSD/6–31++G** level.

A possible explanation for this discrepancy could be attributable to the ability of the 2-methoxyphenoxy radical to adopt two different conformations: one with the methyl group directed toward the O• radical centre interacting with a weak hydrogen bond, the other with the methyl group pointing away. DFT calculations have shown that the former conformer is 1.6–1.9 kcal mol⁻¹ more stable than that pointing away from the O• radical centre.^[4b] On these basis the

additive contribution for an *ortho*-OH is calculated to be about 1.4–1.7 kcal mol⁻¹ and the hydrogen bond interaction in **2B**• is estimated to be 7.0–7.3 kcal mol⁻¹, in satisfactory agreement with the CCSD/6–31++G** value.

It should be remarked that the theoretical BDE values are computed in the gas phase. Attempts to estimate the solvent influence on the BDE with a continuum model such as the PCM^[22] method failed. At the PCM/B3LYP/6–31++G**/B3LYP/6–31++G** level the variation in BDE is negligible on going from benzene to *n*-heptane and ethanol—being 0.1 and –0.3 kcal mol⁻¹, respectively—in evident contrast with experimental evidence. For example, the BDE of 3,5-di-*tert*-butylcatechol **1A** has been found to increase significantly (by 1.4 kcal mol⁻¹) on going from benzene to *tert*-butanol.^[2] This is because large variations in BDE in the liquid phase are due essentially to formation of H-bonding. However, the theoretical BDE values can be safely compared with the experimental values obtained in isooctane, since we have shown^[19] that explicit interaction of two molecules of an apolar solvent such as propane with phenol and the phenoxyl radical (supermolecule approach) is negligible, whereas two large variations of the BDE in opposite directions have been computed on employing two molecules of a HBA solvent such as isopropanol and of a HBD solvent such as 1,1,1,3,3,3-hexafluoroisopropan-2-ol, in agreement with experimentation. Unfortunately, calculations by such a simple supermolecule approach cannot be carried out on catechol since there are two interaction sites at short distance.

Conclusion

In conclusion, there seems to be little doubt that 3,5-di-*tert*-butylcatechol and α -tocopherol are characterised by the same O–H bond dissociation enthalpy, this also being supported by their reactivities, which, at least in hydrocarbons, are quite similar. An examination of literature data actually shows that, in reaction with DPPH radicals in hexane at 30°C, **1A** is about three times more reactive than an α -TOH analogue (2,2,5,7,8-pentamethyl-6-hydroxychroman), while in the reaction with peroxy radicals in styrene at 30°C its reactivity is about half that of α -TOH.^[8] The unsubstituted catechol—which, on the basis of the *ortho*-hydroxyl effect computed by Zhang et al. (10.0 kcal mol⁻¹), should have a BDE value lower than of α -tocopherol and thus should be more reactive than the latter, and also in view of the lower steric crowding in the proximity of the OH groups—is instead six time less reactive in styrene solution.^[8] Therefore, even an appropriate analysis of the available kinetic data indicates that the BDE values for catechols calculated by Zhang et al. are unrealistic. Extensive theoretical calculations indicate that half of the discrepancy between the B3LYP/6–31G** BDE value and experiment is due to the absence of diffuse functions on oxygen (B3LYP/6–31+G*). Furthermore, the DFT method with the B3LYP functional underestimates the BDE of catechol with respect to the more reliable ab initio CCSD method. This accounts for the other half of the discrepancy, so that the BDE of cat-

echol determined by the EPR radical equilibration technique is well reproduced by CCSD/6–31+G* calculations in conjunction with the isodesmic approach.^[21]

Experimental Section

Determination of the equilibrium constant K_1 : Deoxygenated isooctane or toluene solutions containing **1A** (0.04–0.15 M) and BHT (0.1–1 M) were sealed under nitrogen in a Suprasil quartz EPR tube. The sample was inserted in the thermostatted cavity of an EPR spectrometer (Bruker ESP 300) and photolysed with the unfiltered light from a 500 W high-pressure mercury lamp. The temperature was controlled with a standard variable temperature accessory and was monitored before and after each run with a copper–constantan thermocouple. The molar ratio of the two equilibrating radicals was obtained from the EPR spectra and used to determine the equilibrium constant K_1 , by introduction of the initial concentrations of the two reactants into Scheme 1. Initial concentrations were high enough to avoid significant consumption during the course of the experiment. Relative radical concentrations were determined by comparison of the digitised experimental spectra with computer-simulated ones. In these cases an iterative least-squares fitting procedure based on the systematic application of the Monte Carlo method was performed in order to obtain the experimental spectral parameters of the two species, including their relative intensities.^[4a]

FT-IR measurements: The FT-IR spectra were measured from 4000 to 3000 cm⁻¹ with a Nicolet Protégé 460 spectrometer with a resolution of 2 cm⁻¹. Tetrachloromethane solutions of catechol **1A** (0.1 M) were examined in a sealed KBr cell with 0.1 mm optical path.

Computational details: DFT calculations employing the B3LYP functional^[23,24] were carried out on catechol (isomers **2A** and **2C**) and on the parent semiquinone radical (isomers **2B**• and **2C**•) by use of the GAUSSIAN98 system of programs.^[25] Calculations were also performed on phenol and phenoxyl radical to estimate the BDE values by the isodesmic approach [Eq. (2)], using $\text{BDE}_{\text{exp}}(\text{Ph-OH}) = 87.6$.^[4a] Unrestricted wavefunction was used for radical species. Geometries and BDE values were computed with different basis sets. Firstly, a valence double- ζ basis set supplemented with polarisation d-functions on heavy atoms^[26] (6–31G*) and also polarisation p-functions on hydrogens (6–31G**) was employed. Standard diffuse functions^[27] were then added to heavy atoms (6–31+G*) and also to hydrogens (6–31++G**). Finally, calculations were performed by employing a triple- ζ basis^[28] set supplemented with both polarisation and diffuse functions (6–311++G**). The BDE values were also estimated by the coupled-cluster method with single and double excitations (CCSD).^[29] The core electron were held frozen in estimation of electron correlation, since their inclusion would not be expected to influence the optimum geometries significantly. DFT calculations were also performed on the 3,5-di-*tert*-butylcatechol **1A** and on the parent semiquinone radical (isomers **1A**• and **1B**•) at the B3LYP/6–31G* and B3LYP/6–31++G** levels to compute the BDE, the relative stability of the radical isomers, and the barrier to **1A**• \rightarrow **1B**• isomerisation. DFT and CCSD energies were corrected for the zero point vibrational energies (ZPVEs) computed at the B3LYP/6–31G* level by frequency calculations using a scaling factor of 0.9806 to account for anharmonicity.^[30]

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