Investigation of the Influence of Hydroxy Groups on the Radical Scavenging Ability of Polyphenols

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Recently, O−H bond dissociation enthalpies (BDEs) have been successfully used to express the free radical scavenging ability of polyphenolic antioxidants. In this work, the BDEs of phenol, catechol, resorcinol, hydroquinone, pyrogallol, phloroglucinol, 1,2,4-benzenetriol, and 5-hydroxypyrogallol have been calculated at B3LYP/6-311G++(3df, 3pd) and used to elucidate the effect of OH groups. Increasing the number of OH groups in the adjacent (vicinal) position decreases the BDE of phenols. Increasing the number of O−H groups in the alternative position C(1,3) as in resorcinol and C(1,3,5) as in phloroglucinol does not show any notable change in the BDEs when compared to that of OH in C(1) as in phenol. 5-Hydroxypyrogallol has the smallest BDE (250.3 kJ mol^{-1}) followed by pyrogallol (289.4 kJ mol^{-1}), then 1,2,4-benzenetriol (294.8 kJ mol^{-1}), and then catechol (312.8 kJ mol^{-1}). Overall, our results indicated that the presence of ortho and para hydroxy groups reduces the BDEs. An intramolecular hydrogen bond (IHB) develops due to the ortho arrangement of OH's and plays a dominant role in decreasing the BDEs. This key study on phenols showed that the reactive order of OH position in the benzene ring is the following: 5-hydroxypyrogallol > pyrogallol > 1,2,4-benzenetriol > catechol > hydroquinone ≫ phenol ∼ resorcinol ∼ phloroglucinol.

1. Introduction

Polyphenolic antioxidants are the subject of intense scientific research because of the way they work to prevent or lower the risk of various cancers.[1] Cancer caused or induced by free radicals can be effectively scavenged by polyphenols.[2] The excellent scavenging property of polyphenols is attributed to the phenolic OH's present in the ring structures.[3−5] Flavonoids are the most common and widely distributed group of polyphenols. As shown in Figure 1, flavonoids share the common structure of two benzene rings, A and B, on either side of a carbon ring, C, but they are classified differently according to the various combination of the substitutional groups such as OH attached to these structures.[6,7]

The radical scavenging ability of polyphenols depends on its individual structure. It is time-consuming to evaluate the structural effectiveness of antioxidants individually, as researchers have so far identified over 8000 as polyphenols.[2] Instead, model compounds that contribute to most of the polyphenolic structures can be chosen to study and interpret the structural activity. Recently, the potential importance of the number and arrangement of OH groups in polyphenols in drug absorption study across biomembranes has also been recognized.[8] Hence, in this study, we decided to elucidate the effect of OH with respect to the position and number toward radical scavenging ability. Therefore, on the basis of the number and position of OH groups in the benzene ring, phenol (**1**), catechol (**2**), resorcinol (**3**), hydroquinone (**4**), pyrogallol (**5**), phloroglucinol (**6**), 1,2,4-benzenetriol (**7**), and 5-hydroxypyrogallol (**8**) were selected. Importantly, they are also observed as a nucleus in most of the flavonoids.[4]

Free radical scavenging activity of polyphenols (ArO−H's) is characterized by its hydrogen atom donating ability[9] to scavenge the radicals (ROO•):

$$\mathrm{ArO{-}H + ROO\bullet \rightarrow ROO{-}H + ArO\bullet} \qquad (1)$$

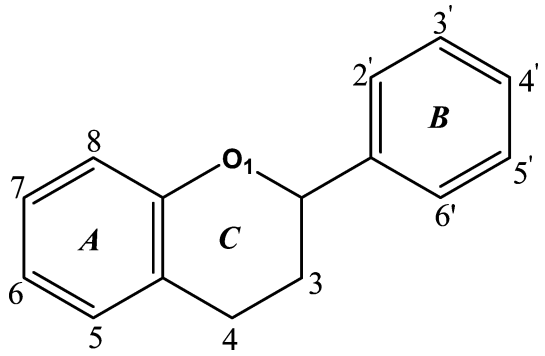

Figure 1. Basic structure of flavonoids.

The ability to donate a hydrogen atom is mainly governed by the O−H bond dissociation enthalpy (BDE).[10] To the best of our knowledge, no comprehensive computational study has been carried out on the BDEs of polyphenols in order to clarify the discrepancy over the number and position of OH's. BDEs have long been successfully computed using density functional theory (DFT) methods,[11] an approach we adopt in this work.

2. Methods

2.1. Theoretical Measurement of BDE. All gas phase calculations were carried out using the B3LYP method and the basis sets 6-31G(d), 6-31+G(d, p), 6-311+G (3df, 2p), and 6-311++G (3df, 3pd), as implemented in the Gaussian 98 program package.[12] This functional has been shown to provide accurate geometries for phenolic systems.[11] Full geometry optimizations and frequency calculations were performed using

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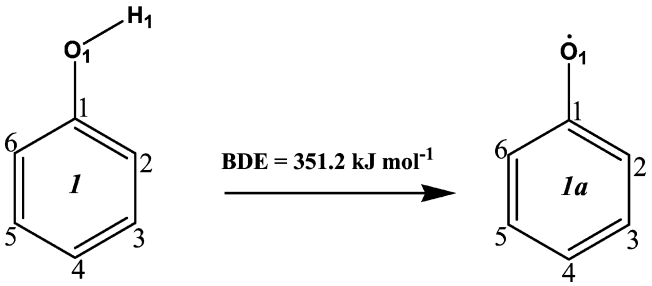

Figure 2. BDE using B3LYP/6-311G++(3df, 3pd) for phenol and its radical.

Figure 3. BDE using B3LYP/6-311G++(3df, 3pd) for catechol and its radical.

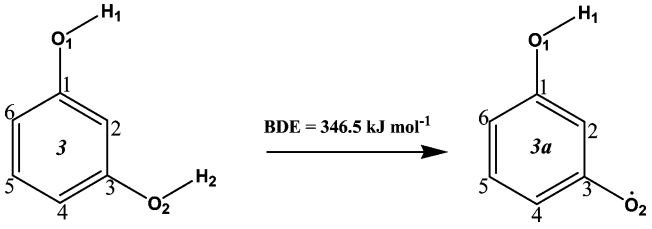

Figure 4. BDE using B3LYP/6-311G++(3df, 3pd) for resorcinol and its radical.

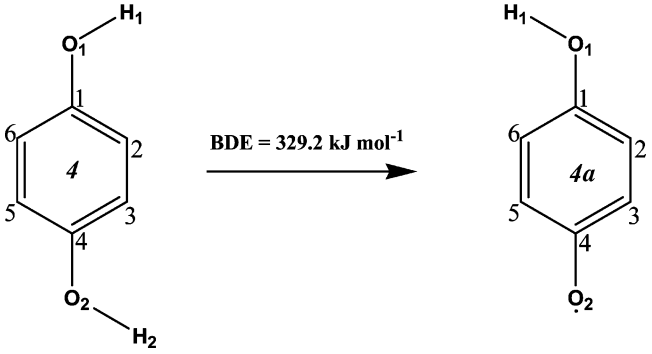

Figure 5. BDE using B3LYP/6-311G++(3df, 3pd) for hydroquinone and its radical.

the restricted B3LYP method for the parent molecule and the unrestricted B3LYP method for the radical. The BDEs at 298.15 K were calculated using eq 2, for the most stable ArOH conformer and the weakest ArO−H bond.

$$\mathrm{BDE(O{-}H)} = H(\mathrm{Ar{-}O\bullet}) + H(\mathrm{H}) - H(\mathrm{ArO{-}H}) \quad (2)$$

$H(j)$ in eq 2 is the enthalpy of chemical j at 298.15 K and 1 atm. As has been done in others' work,[13,14] we have used the exact (0 K) enthalpy, H(H), of the hydrogen atom (−0.5 au) for the BDE calculations.

The most stable ArOH compound was assumed to be that conformer which, if possible, could form one or more intramolecular hydrogen bonds (IHBs). The conformers that were chosen are given in Figures 2−9. Furthermore, eq 2 requires us to establish which ArOH bond is the weakest, since the

Figure 6. BDE using B3LYP/6-311G++(3df, 3pd) for phloroglucinol and its radical.

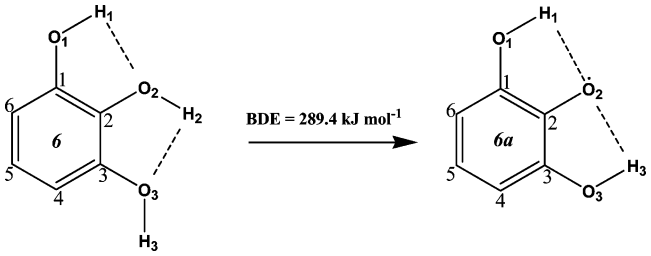

Figure 7. BDE using B3LYP/6-311G++(3df, 3pd) for pyrogallol and its radical.

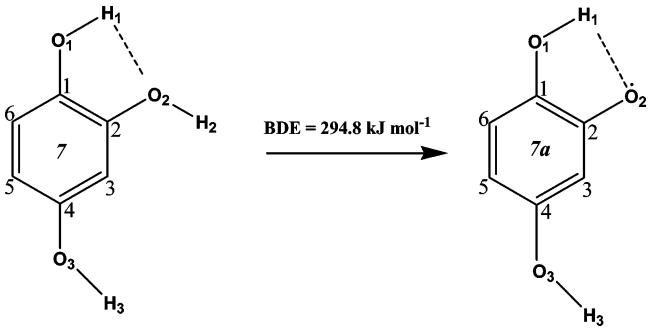

Figure 8. BDE using B3LYP/6-311G++(3df, 3pd) for 1,2,4-benzenetriol and its radical.

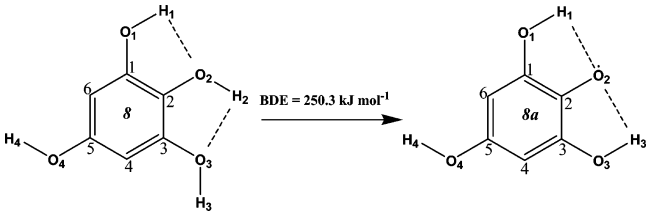

Figure 9. BDE using B3LYP/6-311G++(3df, 3pd) for 5-hydroxypyrogallol and its radical.

weaker the O−H bond, the smaller the BDE and the greater the free radical scavenging ability of the antioxidant. We determined the weakest ArO−H bond by computing the BDE for all OH sites at the B3LYP/6-31G(d) level. The weakest O−H bond was determined as that giving rise to the smallest BDE. After identifying the weakest OH site in all of the compounds, a comparison between the BDE computed using the above-mentioned four basis sets was performed. The BDEs obtained were found to converge to within 2 kJ mol^{-1} at the 6-311++G-(3df, 3pd) level, and were also in agreement with the experimental gas phase[15] value for phenol to within 9 kJ mol^{-1}. In addition, the geometry of phenol (Table 1) at 6-311++G(3df, 3pd) was found to be close to the experimental value.[16]

Since the experimental structure is not available for the phenoxide radical (**1a**), we compared our geometry with that of other theoretical studies (Table 2). The calculated intramolecular distances in the phenoxide radical (**1a**) were close to the literature values.[17] The expectation values of the spin squared operator for all of our radicals was found to lay between 0.78 and 0.79, close to the expected value of 0.75 for a pure doublet

TABLE 1: Comparison of the Bond Length (Å) of Optimized Phenol in the Gas Phase with Experimental and Other Theoretical Methods

phenol (**1**)			
bond length	B3LYP/ 6-311++G(3df, 3pd)	experiment[a]	B3LYP/ 6-31+G(3pd)[b]
R(C1−C2)	1.390	1.391	1.400
R(C2−C3)	1.390	1.392	1.402
R(C3−C4)	1.387	1.395	1.401
R(C4−C5)	1.390	1.395	1.404
R(C5−C6)	1.390	1.394	1.399
R(C1−C6)	1.390	1.391	1.399
R(C1−O)	1.360	1.375	1.403
R(O−H)	0.960	0.957	1.081
R(C2−H)	1.080	1.081	1.081
R(C3−H)	1.080	1.084	1.081
R(C4−H)	1.080	1.080	1.080
R(C5−H)	1.080	1.084	1.081
R(C6−H)	1.080	1.086	0.966

[a] See ref 16. [b] See ref 26.

TABLE 2: Comparison of the Bond Length (Å) of Optimized Phenoxide Radical in the Gas Phase with Other Theoretical Methods

phenoxide radical (**1a**)			
bond length	B3LYP/ 6-311++G(3df, 3pd)	CAS-SCF/ 6-311G(2d, p)[c]	B3LYP/ 6-31+G(3pd)[b]
R(C1−C2)	1.450	1.454	1.443
R(C2−C3)	1.370	1.370	1.386
R(C3−C4)	1.440	1.411	1.413
R(C1-O•)	1.240	1.228	1.298
R(C2−H)	1.080	1.073	1.081
R(C3−H)	1.080	1.074	1.081
R(C4−H)	1.080	1.073	1.081

[b] See ref 26. [c] See ref 17.

wave function. Henceforth, we will consider only the results for the BDE at the 6-311++G(3df, 3pd) level.

It should be noted that in situ antioxidant reactions occur in the condensed phase. Hence, BDE calculations were carried out using a continuum solvent model. The self-consistent reaction field (SCRF) model[18] was used for the BDE calculation at the 6-311++G(3df, 3pd) level in polar protic (methanol; ethanol), polar aprotic (acetonitrile; acetone), and apolar (tetrahydrofuran) solvents for phenol, catechol, resorcinol, hydroquinone, pyrogallol, phloroglucinol, and 1,2,4-benzenetriol. However, it was noted from the calculations that the SCRF model showed only slight differences (1−2 kJ mol^{-1}) in BDE among the solvents studied.

Henceforth, we will focus our attention on the results for all of the phenolic compounds that we obtained at the gas phase B3LYP/6-311++G(3df, 3pd) level in order to explain the influence of OH's.

3. Results and Discussion

The BDEs of all of the phenols at the B3LYP/6-311++G(3df, 3pd) level are presented in Table 3. Also included in Table 3 are the experimental values, where available. Our computed BDEs are consistently below the experimental values. This is, perhaps, in part due to the unrestricted method used for computing the radical energy. While our wave functions contain very little spin contamination, the generally lower energy of the unrestricted results for the radicals yields a generally lower prediction for the BDEs. One approach would be to compute the energies of the radicals via a restricted open-shell method. This approach, however, will likely not completely alleviate the issue, since our unrestricted wave functions are virtually

TABLE 3: B3LYP/6-311++G(3df, 3pd) Gas Phase BDEs (in kJ mol^{-1}) for Phenols (the BDE of Phenol (1) Was Calculated as 351.2 kJ mol^{-1})

position of OH's	phenols	BDE	ΔBDE_1[a]	BDE_{expt}
phenol		351.218	0.00	359.8[i]
meta effects	Res,[c] **3**	346.450	−4.78	
	Phl,[e] **5**	353.996	−2.78	371.4[j]
ortho (IHB)	Cat,[b] **2**	312.849	−38.37	342.3[k]
	Pyr,[f] **6**	289.385	−61.89	328.9[j]
para effect	HQ,[d] **4**	329.228	−21.99	335[l]
combined (ortho and para)	Benz,[g] **7**	294.849	−56.37	
	HP,[h] **8**	250.280	−100.9	

[a] $\Delta BDE_1 = BDE_{phenol} - BDE_{ArOH}$. [b] Catechol (**2**). [c] Resorcinol (**3**). [d] Hydroquinone (**4**). [e] Phloroglucinol (**5**). [f] Pyrogallol (**6**). [g] 1,2,4-Benzenetriol (**7**). [h] 5-Hydroxypyrogallol (**8**). [i] Reference 15. [j] Reference 22. [k] Reference 23. [l] Reference 31.

uncontaminated. For instance, we optimized the geometry of phenol and catechol at the ROB3LYP/6-311++G(3df, 2pd) level and found the equilibrium energies were higher than their unrestricted counterparts by 9.45 and 6.30 kJ mol^{-1}, respectively. However, our unrestricted calculations differ from the experimental BDE by 8.6 and 29.4 kJ mol^{-1}, respectively.

Another procedure that can partially account for this is via an isodesmic approach and has been utilized by other workers for systems such as those studied in this work.[19,27] This procedure utilizes the expression

$$BDE(ArO-H) = BDE_{exper}(phenol) + \{H(Ar-O\bullet) - H(ArOH)\} - \{H(PhO\bullet) - H(phenol)\} \quad (3)$$

Such a procedure results in simply adding the difference between the experimental and calculated BDEs of phenol to all of the BDEs computed for other species. At the B3LYP/6-311++G(3df, 3pd) level, this amounts to 8.6 kJ mol^{-1}. Thus, if we were to use eq 3 to compute our BDE, we would need to add 8.6 kJ mol^{-1} to all of the BDE values given in Table 3. Note, however, that the values given in the column entitled ΔBDE_1 are unchanged, and it is such differences that we focus on throughout the rest of this paper.

One further point should be noted, and that is the current debate regarding the best computational method for computing BDEs to chemical accuracy (results within 4 kJ mol^{-1} of experiment). The discussion[20,21] reveals difficulties in obtaining accurate BDEs because (i) much dispute exists on the precise experimental values and (2) there is no consensus on the theoretical method that gives the most accurate BDEs. However, we note here that DFT methods, especially the B3LYP functional, tend to underestimate BDEs, although differences in BDEs should be more accurate.

By examination of Table 3, it was noted that the BDEs were mainly influenced by the presence of both the ortho position and para position of OH, and these effects are discussed in detail below.

3.1. Ortho (IHB) Effect. As shown in Table 3, the BDE of catechol (*ortho*-2-hydroxy benzene) was calculated to be 312.8 kJ mol^{-1}. In catechol, the ortho arrangement of the OH groups leads to the development of an intramolecular hydrogen bond (IHB). Hence, the radical (see Figure 3) from catechol (**2a**) is more stable than the phenoxide radical (**1a**). This can account for the smaller BDE of catechol as compared to that of phenol. As is clearly shown in Figure 10, an ortho OH in phenol can reduce the BDE by about 38.4 kJ mol^{-1}. This relative BDE is also found to be closer to the experimental (30.1 kJ mol^{-1})[23] and other theoretical (34.5 kJ mol^{-1})[24] values. Thus, the ortho arrangement of OH's makes catechol a better radical scavenger than phenol.

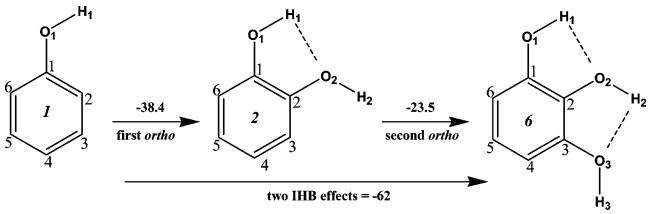

Figure 10. IHB effects on phenol and catechol (the values above the arrows are the changes in the BDE in kilojoules per mole).

Figure 11. Two IHB effects on resorcinol (the value below the arrow is the change in the BDE in kilojoules per mole).

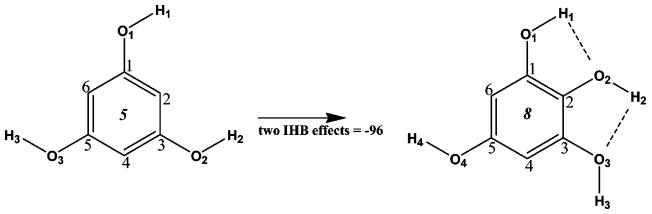

Figure 12. Two IHB effects on phloroglucinol (the value below the arrow is the change in the BDE in kilojoules per mole).

Among the two and three OH compounds studied, the smallest BDE (289.4 kJ mol^{-1}) was observed for pyrogallol, which has OH's in the C(1,2,3) positions of the benzene ring. Our value is close to the literature value (304.2 kJ mol^{-1}) reported by Wright et al.[25] and lower than the values reported by Bakalbassis et al. (323.8 kJ mol^{-1}) at 6-31+G(3pd)[26] and by Hong et al. (322.7 kJ mol^{-1})[27] at CCSD/6-31+G(d). In our study, for both pyrogallol and 5-hydroxypyrogallol, the middle OH was considered broken to donate H atom, as it is believed that both sides of OH could provide more stability to the radical in the center. (Our B3LYP/6-31G(d) calculations mentioned previously for the BDE of all the OH's also indicated that the middle OH was the weakest.) A recent NMR study[28] also indicated that the peak intensity for C═O was observed for the center OH site of pyrogallol after it had reacted with the free radical. Hence, the equal stability exerted by both side OH's produces the relatively stable radicals **6a** and **8a**.

In Figure 10, it can also be seen that the presence of OH in the C(3) position in pyrogallol introduces the second possibility of IHB formation. The two OH's located at the C(2) and C(3) positions exert two IHBs, which reduces the BDE significantly. Thus, the more IHBs in the structure, the more stable the radical, and thus the smaller the BDE.

Figures 11 and 12 clearly indicate that the introduction of OH in the C(2) of resorcinol as well as phloroglucinol provides two possible IHBs in their structures, respectively named pyrogallol and 5-hydroxypyrogallol. The relative BDE of pyrogallol to resorcinol is estimated as 64.6 kJ mol^{-1} and 5-hydroxypyrogallol to resorcinol is about 96 kJ mol^{-1}. These results confirm that the ortho bridge (IHB) has a great influence on BDEs and hence the free radical scavenging ability.

As shown in Figure 13, resorcinol can be modified to 1,2,4-benzenetriol through the addition of an OH in either the C(6) or C(4) position in resorcinol. Our calculations show that the BDE of 1,2,4-benzenetriol is smaller by 51.6 kJ mol^{-1} than that of resorcinol.

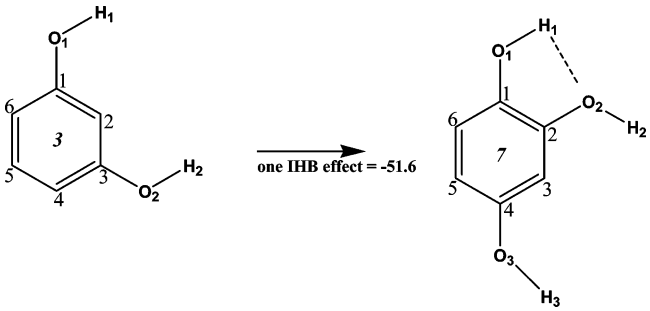

Figure 13. One IHB effect on resorcinol (the value below the arrow is the change in the BDE in kilojoules per mole).

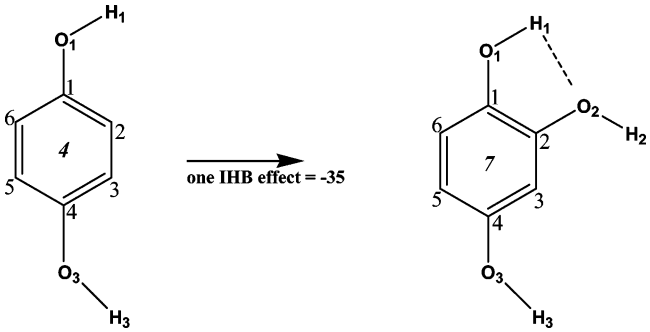

Figure 14. One IHB effect on hydroquinone (the value below the arrow is the change in the BDE in kilojoules per mole).

Similarly, introducing the IHB effect by placing an OH in the C(2) position of hydroquinone may lead to the compound called 1,2,4-benzenetriol, whose BDE is lower than that of hydroquinone by 35 kJ mol^{-1}. This is shown in Figure 14.

Overall, it can be stated from the gas phase studies that introducing ortho hydroxyls generates an IHB in the structure and plays a vital role in the BDEs and thus free radical scavenging ability. This supports the statements made by Barclay et al.[29] and Burton et al.[30] that the main factor controlling BDEs of most of the flavonoids is the stabilization by the IHB.

3.2. Para Effect. The BDE of hydroquinone (*para*-2-hydroxy benzene) was calculated as 329.2 kJ mol^{-1}, which is lower by 6 kJ mol^{-1} as compared to the experimental value.[31] Even though IHB is absent in both resorcinol and hydroquinone, the BDE of hydroquinone is found to be smaller than that of resorcinol and phenol by 17.2 and 22 kJ mol^{-1}, respectively. This implies that the OH at the para position reduces the BDE of phenol considerably, whereas the OH at the meta position of phenol does not have any strong effect on the BDE. These findings support the argument[32] that electron donating groups (here as OH) at the meta position do not have any significant effect on the bond strength in comparison to the unsubstituted phenol, whereas the same at the para position reduces the O−H bond strength significantly. The BDE of hydroquinone was also found to be larger than that of catechol by 16.4 kJ mol^{-1}. This shows that the second OH in the para position has more radical scavenging activity than that in the meta position of phenol but certainly less than that of the ortho effect exerted due to the IHB.

3.3. Combined Effects of Ortho (IHB) and Para. Placing one ortho and para OH in phenol produces the structure of 1,2,4-benzenetriol. Calculations show that the relative BDE of 1,2,4-benzenetriol to phenol is about 56.4 kJ mol^{-1}. Comparing this value with the relative BDE of catechol to phenol (38.4 kJ

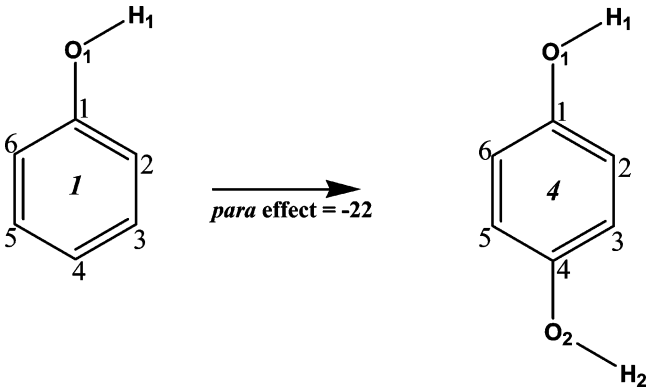

Figure 15. Para effect on phenol (the value below the arrow is the change in the BDE in kilojoules per mole).

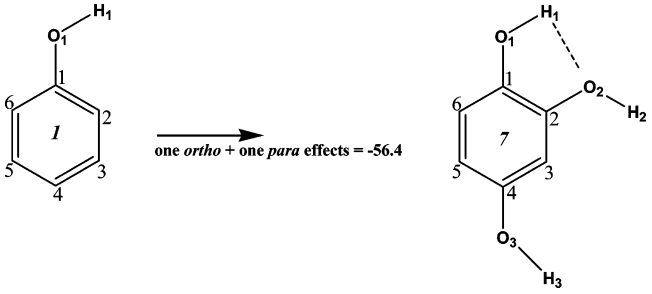

Figure 16. Combined effects of phenol to 1,2,4-benzenetriol (the value below the arrow is the change in the BDE in kilojoules per mole).

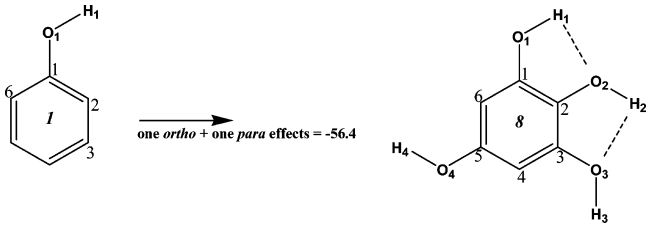

Figure 17. Combined effects of phenol to 5-hydroxypyrogallol (the value below the arrow is the change in the BDE in kilojoules per mole).

mol^{-1}) and hydroquinone to phenol (22 kJ mol^{-1}), it can be understood that the combined effect of both ortho and para may reduce the BDE significantly. 5-Hydroxypyrogallol has two IHBs and one para with respect to the C(2) position. Examining the relative BDE of 5-hydroxypyrogallol to phenol (100.9 kJ mol^{-1}) also confirms the importance of the combined effect. On comparing the BDE of phenol to the one ortho and one para OH structured compound (1,2,4-benzenetriol) and to the two ortho and one para OH structured compound (5-hydroxypyrogallol), it can be said that ortho plays a dominating role in reducing the BDE. This is clearly shown in Figure 16.

3.4. Meta Effect. The BDE of resorcinol(*meta*-2-hydroxy benzene) was calculated as 346.5 kJ mol^{-1}, which is larger than that of catechol by 33.6 kJ mol^{-1} but close to that of phenol by only 4.8 kJ mol^{-1}. This result shows that the second OH in the C(3) position of the phenol (two O−H's in the meta position) does not have much of an effect on the BDE of phenols and is almost equal to the one hydroxy compound (phenol). Table 3 shows that the BDE of phloroglucinol, which has OH's in the C(1,3,5) position, is estimated to be 353.9 kJ mol^{-1}. Interestingly, the relative BDE for phloroglucinol to phenol (2.8 kJ mol^{-1}) indicates that it is very close to that of phenol and higher than that of the meta 2-OH compound (resorcinol) by only 7.5 kJ mol^{-1}. Of all the compounds studied, BDE is the highest for phloroglucinol, which has three OH's in number. This result emphasizes that the radical scavenging ability of polyphenols depends mainly on the positioning of OH's and certainly *not on its number*.

Among the two, three, and four OH group compounds studied, catechol, pyrogallol, and 5-hydroxypyrogallol have the smallest BDEs. This result confirms that only the position of the OH group is important for determining the BDE. The BDE of phenols decreases in the following order: 5-hydroxypyrogallol > pyrogallol > 1,2,4-benzenetriol > catechol > hydroquinone $\gg$ resorcinol $\sim$ phloroglucinol $\sim$ phenol. Our findings on the order of radical scavenging ability are also in good agreement with the NMR conformational studies[28] on the polyphenols. Hence, our DFT study on gas phase BDE provides more evidence for the importance of the catechol moiety (pyrogallol, 1,2,4-benzenetriol) among all other substitutional groups on the B and C rings of flavonoids.[11,33]

4. Conclusion

We have presented computational results on the phenols to provide a deeper understanding of the effect of OH's with respect to position and numbers in BDE calculations. We conclude on the basis of our BDE that the relative activity position of OH in the benzene ring is

$$C(1,2,3,5) > C(1,2,3) > C(1,2,4) > C(1,2) > C(1,4) > C(1) \sim C(1,3) \sim C(1,3,5)$$

This study also concludes that the vicinal trihydroxy moiety (5-hydroxypyrogallol and pyrogallol) is superior to that of the ortho dihydroxy moiety (1,2,4-benzenetriol and catechol). Hence, there is every reason to believe that the ortho OH moiety can play a significant role in radical-trapping ability.

Overall, two points seem clear: (i) The position of OH's is very important for lower BDEs but not the number of OH's. (ii) Increasing the number of OH's in the vicinal (ortho) position, that is, more IHBs, decreases the BDEs, but increasing the number of OH's in the meta position has little impact on BDEs compared with phenol; OH in the para position also lowers the BDEs, and hence, the largest radical scavenging activity is expected for 5-hydroxypyrogallol.

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