

Theoretical Calculation of Substituent Effects on the O–H Bond Strength of Phenolic Antioxidants Related to Vitamin E

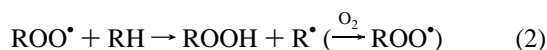
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Abstract: Calculations on phenol and a large number of phenols substituted with methyl, methoxyl, and amino groups have yielded reliable gas-phase O–H bond dissociation energies, BDE(ArO–H)^{gas}. Geometries for the phenol, ArOH, and aryloxy radical, ArO, were optimized at the (semiempirical) AM1 level followed by single point density functional theory (DFT) calculations using a 6-31G basis set supplemented with p-functions on the hydrogen atom and the B3LYP density functional. This gave BDE(PhO–H)^{gas} = 86.46 kcal/mol, which is in good agreement with the experimental value of 87.3 ± 1.5 kcal/mol. All but one of the compounds and conformations examined had weaker O–H BDE's than phenol, the exception being *o*-methoxyphenol with the O–H group pointing toward this substituent (BDE = 87.8 kcal/mol). Where comparison was possible, calculated differences in O–H BDE's were in excellent agreement with experiment (better than 1 kcal/mol). A simple group additivity scheme also gave excellent agreement with calculated BDE (ArO–H)^{gas} values. Some potential new leads to phenolic antioxidants more active than vitamin E have been uncovered.

All organic materials exposed to air undergo oxidative degradation. Reducing the rate of such degradation by utilizing low concentrations of "antioxidants" is important for all aerobic organisms and for many commercial products. Phenols are an extremely important class of antioxidants. They owe their activity to their ability to trap the chain-carrying peroxy radicals by donation of the phenolic hydrogen atom, reaction 1, which is a very much faster reaction than the attack of the peroxy radicals on the organic substrate, reaction 2. For example, a



phenol, α -tocopherol (vitamin E), is the major lipid-soluble, peroxy radical-trapping antioxidant in human blood plasma^{1,2} and in normal and cancerous tissues.³ This phenol has almost the optimum structure (i.e., pattern of alkyl and alkoxy moieties substituted on the phenol's aromatic ring) required to maximize the rate of reaction 1.^{1,4}

Of course, a high rate for reaction 1 is expected to go hand in hand with a low O–H bond dissociation energy (BDE). Considerable effort has therefore been devoted to the measurement of O–H BDE's for phenols with a variety of different experimental techniques.⁵ Although some of these techniques are generally applicable and yield relatively reliable differences in phenolic O–H BDE's, none of them combine speed with experimental simplicity to yield reliable absolute O–H BDE's. Theoretical calculations, on the other hand, might provide a rapid, simple, and reliable method for determining phenolic O–H BDE's. The overwhelming advantage of a theoretical approach is that not only should it help to interpret observed substituent effects on "known" phenolic O–H BDE's but also it could be used to predict BDE's for phenols having novel structural features that are not amenable to any experimental procedure. Such interesting phenols would include the two isomers of phenols substituted with a single *ortho* substituent (i.e., with the OH group pointing toward the substituent and with the OH group pointing away), for which experiment can only yield an averaged O–H BDE, and phenols substituted with heteroatoms containing labile hydrogen atoms, e.g., the NH₂ or SH groups, for which most experimental techniques will yield only the weakest X–H BDE in the molecule. We report herein a density functional theoretical method for calculating gas-phase O–H BDE's for phenols (BDE (ArO–H)^{gas}). Our calculated BDE's are in very satisfactory agreement in their absolute values with "known" BDE's and are in outstandingly good agreement with the "known" effect of substituents on BDE differences.

Method of Calculation

The program GAUSSIAN-94¹² was used for all calculations described in this paper. First, a lower level of theory was used to obtain optimized geometries and vibration frequencies for both the phenol

(5) E.g., calorimetry⁶ and ESR measurements of equilibrium constants⁷ for phenols yielding persistent phenoxyl radicals and, more generally, electrochemical methods⁸ and photoacoustic calorimetry.^{9–11}

(6) Mahoney, L. R.; Ferris, F. C.; DaRooge, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 3883–3889.

(7) Lucarini, M.; Pedulli, G. F.; Cipollone, M. *J. Org. Chem.* **1994**, *59*, 5063–5070.

[†] Carleton University.

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[®] Abstract published in *Advance ACS Abstracts*, April 1, 1997.

(1) For a review, see: Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194–201.

(2) Burton, G. W.; Joyce, A.; Ingold, K. U. *Lancet* **1982**, August, 751. Burton, G. W.; Joyce, A.; Ingold, K. U. *Arch. Biochem. Biophys.* **1983**, *221*, 281–289. Ingold, K. U.; Webb, A. C.; Witter, D.; Burton, G. W.; Metcalf, T. A.; Muller, D. P. R. *Arch. Biochem. Biophys.* **1987**, *259*, 224–225.

(3) Cheeseman, K. H.; Burton, G. W.; Ingold, K. U.; Slater, T. F. *Toxicol. Pathol.* **1984**, *12*, 235–239. Cheeseman, K. H.; Collins, M.; Proudfoot, K.; Slater, T. F.; Burton, G. W.; Ingold, K. U. *Biochem. J.* **1986**, *235*, 507–514. Cheeseman, K. H.; Emery, S.; Maddix, S. P.; Slater, T. F.; Burton, G. W.; Ingold, K. U. *Biochem. J.* **1988**, *250*, 247–252. Slater, T. F.; Cheeseman, K. H.; Benedetto, C.; Collins, M.; Emery, S.; Maddix, S. P.; Nodes, J. T.; Proudfoot, K.; Burton, G. W.; Ingold, K. U. *Biochem. J.* **1990**, *265*, 51–59.

(4) (a) Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6472–6477. (b) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053–7065. (c) Ingold, K. U.; Burton, G. W.; Foster, D. O.; Zuker, M.; Hughes, L.; Lacelle, S.; Luszyk, E.; Slaby, M. *FEBS Lett.* **1986**, *205*, 117–120.

(ArO–H) and the radical (ArO). This was followed by a higher level of theory to obtain the electronic energy. Since some of the molecules in this study are rather large and it is desirable to be able to use the same methods for even larger systems, a preliminary study was done to establish the generality of our approach. The most time-consuming part of the calculation, namely the geometry optimization and determination of the vibration frequencies, was done using the semiempirical AM1 method.¹³ Comparison of the AM1 geometries with known experimental values for phenol¹⁴ and other reference data for the phenoxyl radical shows that the AM1 geometries are sufficiently accurate for our purposes.

Electronic energies were obtained by means of density functional theory (DFT) using the B3LYP functional.¹⁵ Four “basis set experiments” were performed with DFT, including the 6-31G basis (split-valence) the 6-31G(d) basis (adding polarization functions on the heavy atoms), the 6-31G(d,p) basis (polarization functions on heavy atoms and H) and finally the 6-31G(p) basis (polarization functions only on H). The latter basis set provided the best combination of size and accuracy. Optimization of the *p*-exponent on hydrogen showed that the value 1.0 gave a lower total energy for phenol than the normal value of 0.75; the value 1.0 was therefore used to calculate the total energy. The final calculation/basis for the electronic energy is denoted B3LYP/6-31G(p'), where the p' indicates that the normal basis has been modified.

Experimental values quoted in this study are bond dissociation enthalpies (BDE's) at 298 K, so it is necessary to correct the computed electronic energy values for zero-point energies as well as translational, rotational, and vibrational contributions to the enthalpy. Traditionally, the zero-point energies must first be scaled to reflect the difference between the (harmonic) computed frequencies and the actual (anharmonic) experimental frequencies. For this purpose, a scale factor was derived for the AM1 zero-point energy by comparison to the known experimental frequencies of phenol. Thermochemical corrections are then applied to the following generic reaction, phenol → phenoxyl + H. Such corrections are normally done (e.g., as in GAUSSIAN-94) to the energy by adding the scaled zero-point energy to the electronic energy, then adding (3/2)RT for translation to each species, plus an additional (3/2)RT for rotation for phenol and phenoxyl. An additional correction is included to account for excitation of the vibrations in phenol and phenoxyl at a temperature of 298.15 K, giving E_{298}^0 . This latter correction can be problematic in the case of very low frequency vibrations, possibly giving excessive importance to the particular low-frequency modes obtained with the AM1 method. It was thought that more accurate results would be obtained by omitting this vibrational excitation correction; this results in a small systematic error of ca. 0.1 kcal/mol, which will be discussed in context. Finally, adding an additional RT to all three species converts E_{298}^0 into H_{298}^0 . The

(8) (a) Bordwell, F. G.; Cheng, J.-P.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 1229–1231. (b) Lind, J.; Shen, X.; Eriksen, T. E.; Merényi, G. *J. Am. Chem. Soc.* **1990**, *112*, 479–482. (c) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1991**, *113*, 1736–1743. (d) Parker, V. D. *J. Am. Chem. Soc.* **1992**, *114*, 7458–7462. (e) Wayner, D. D. M.; Parker, V. D. *Acc. Chem. Res.* **1993**, *26*, 287–294.

(9) Mulder, P.; Saastad, O. W.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 4090–4092.

(10) Wayner, D. D. M.; Luszyk, E.; Pagé, D.; Ingold, K. U.; Mulder, P.; Laarhoven, L. J. J.; Aldrich, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 8737–8744.

(11) Wayner, D. D. M.; Luszyk, E.; Ingold, K. U.; Mulder, P. *J. Org. Chem.* **1996**, *61*, 6430–6433.

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gompers, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1995.

(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

(14) Lide, D. R., Ed. *CRC Handbook of Chemistry and Physics*, 75th ed.; CRC Press: Boca Raton, FL 1994; p 9–37.

(15) Stevens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785–789. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377.

Table 1. Comparison of Internuclear Distances at the Optimized Geometry for Phenol, Determined by Various Theoretical Treatments (All Bond Lengths in Å)

bond length	BLYP ^a	B3LYP	B3LYP	B3LYPA ^a	AM1	expt ^b
	6-31G(d)	6-31G(d,p)	6-31G(p')	6-311G(d,p)		
R(C ₁ C ₂)	1.410	1.397	1.401	1.397	1.402	1.391
R(C ₂ C ₃)	1.403	1.396	1.401	1.390	1.394	1.392
R(C ₃ C ₄)	1.408	1.395	1.400	1.395	1.394	1.395
R(C ₄ C ₅)	1.405	1.398	1.403	1.392	1.397	1.395
R(C ₅ C ₆)	1.406	1.393	1.397	1.393	1.391	1.394
R(C ₁ C ₆)	1.410	1.399	1.401	1.396	1.405	1.391
R(C ₁ O)	1.384	1.368	1.395	1.367	1.377	1.375
R(OH)	0.981	0.966	0.967	0.962	0.968	0.957
R(C ₂ H)	1.093	1.088	1.086	1.083	1.099	1.081
R(C ₃ H)	1.094	1.086	1.084	1.084	1.100	1.084
R(C ₄ H)	1.093	1.085	1.083	1.083	1.099	1.080
R(C ₅ H)	1.094	1.086	1.084	1.084	1.100	1.084
R(C ₆ H)	1.097	1.085	1.083	1.087	1.099	1.086
error ^c	0.013	0.004	0.007	0.003	0.010	

^a From ref 16. ^b Experimental data from: Larsen, N. W. *J. Mol. Struct.* **1979**, *51*, 175–190. ^c Average absolute deviation (in Å) from experimental values.

difference between products and reactants, ΔH_{298}^0 , subject to the approximation described above, is compared to the experimental BDE's.

Results and Discussion

Phenol (structure **1**) and the phenoxyl radical serve as the reference compounds for these calculations. Table 1 shows a comparison of the optimized geometry of phenol, including a comparison with the experimental values¹⁴ and the recent theoretical calculations of Costa Cabrol *et al.*¹⁶ The B3LYP methods give excellent geometries, with the largest basis sets giving the best results. The average absolute deviation of the 6-31G(p') basis is nevertheless very good at 0.007 Å. The AM1 result is acceptable, with an error of 0.010 Å. It is also important to establish the difference between AM1 and B3LYP/6-31G(p') geometries, which gives the rather small error of 0.010 Å.

No experimental structure exists for the phenoxyl radical, but two careful theoretical studies have been done, by Chipman, Liu, Zhou and Pulay¹⁷ (CLZP) and Qin and Wheeler¹⁸ (QW). The study by CLZP was restricted to the use of traditional *ab initio* methods where the basis set was systematically increased; the largest calculation was a CAS-SCF study using a 6-311G(2d,p) basis set. The study by QW included an identical CAS-SCF/6-311G(2d,p) as well as a variety of DFT methods with a 6-31G(d) basis set. These authors considered the phenoxyl radical to be a stringent test of the various exchange and correlation functionals used in density functional theory, due to the highly delocalized, extensively correlated nature of the radical. In addition, CLZP point out in their introduction that the phenoxyl radical has been a difficult case for theoretical calculations. In particular, due to the possibilities of spin contamination in the wave function and strong nondynamical correlation effects in the π system, the C–O bond distance in previous calculations was found to vary from 1.22 to 1.47 Å depending on the type of calculation used.¹⁷ It is therefore important to calibrate the methods used in our work against both the phenol and the phenoxyl reference structures.

Table 2 presents our calculated optimized geometries of the phenoxyl radical, together with the calculations of QW and CLZP. The variation between the different methods of calculation is reasonably small for all bonds except the C–O bond

(16) Costa Cabrol, B. J. C.; Fonseca, R. G. B.; Simões, J. A. M. *Chem. Phys. Lett.* **1996**, *258*, 436–444.

(17) Chipman, D. M.; Liu, R.; Zhou, X.; Pulay, P. *J. Chem. Phys.* **1994**, *100*, 5023–5035.

(18) Qin, Y.; Wheeler, R. A. *J. Chem. Phys.* **1995**, *102*, 1689–1698.

Table 2. Comparison of Internuclear Distances at the Optimized Geometry for the Phenoxy Radical Determined by Various Theoretical Treatments (All Bond Lengths in Å)

bond length	BLYP ^a 6-31G(d)	B3LYP 6-31G(d,p)	B3LYP 6-31G(p')	CAS-SCF ^{a,b} 6-311G(2d,p)	AM1
R(C ₁ C ₂)	1.465	1.453	1.443	1.454	1.461
R(C ₂ C ₃)	1.388	1.378	1.385	1.370	1.380
R(C ₃ C ₄)	1.420	1.410	1.412	1.411	1.410
R(C ₁ O)	1.270	1.258	1.296	1.228	1.253
R(C ₂ H)	1.093	1.085	1.083	1.073	1.099
R(C ₃ H)	1.094	1.086	1.084	1.074	1.101
R(C ₄ H)	1.094	1.086	1.084	1.073	1.099
error ^c	0.010		0.009	0.011	0.008

^a From ref 18. ^b From ref 17. ^c Average absolute deviation (in Å) from results of the B3LYP/6-31G(d,p) calculation.

where values range from 1.228 to 1.296 Å. It is expected that this C–O bond will have a significant amount of double-bond character, as indicated by resonance structures. However, it seems doubtful that this bond would be as short as the C–O bond in benzoquinone, viz.,¹⁹ 1.225 Å. Instead it would be expected to be intermediate between the benzoquinone value and the single C–O bond distance in phenol (1.375 Å, Table 1). The C–H bonds in the CAS-SCF calculation are also rather short, suggesting that it may be better to use the B3LYP/6-31G(d,p) calculation as a reference. With that choice, all methods give average absolute deviations near 0.01 Å. The AM1 method gives quite a good geometry and can therefore be used for radicals as well as neutral molecules.

The C–O bond calculated with the B3LYP/6-31G(p') basis is 1.296 Å, which is clearly too long. This will introduce a systematic error in the BDE's compared to a calculation which used the optimized geometries obtained with the same B3LYP/6-31G(p') basis (i.e., a fully consistent calculation). The relative error over a family of phenols can be expected to largely cancel out, however, since in all cases we are looking at the conversion from a (substituted) phenol to the corresponding (substituted) phenoxy radical + H. The magnitude of this error will be quantified below.

The AM1 frequencies from the calculation of phenol were compared to the experimental values in order to obtain a suitable scaling factor for the computed frequencies. Experimental frequencies for phenol were reported by Bist, Brand and Williams.²⁰ These frequencies range over the values 244–3656 cm⁻¹. Agreement with the AM1 frequencies at the AM1-optimized geometry is generally within 50 cm⁻¹ except for the O–H stretch which differs by almost 200 cm⁻¹. To obtain an approximation of the experimental zero-point energy (ZPE), the experimental (anharmonic) values were summed and the result divided by two to obtain 22 228 cm⁻¹. The AM1 ZPE is obtained in the same way and is 23 475 cm⁻¹. The scale factor we used was therefore the ratio 22 228/23 475 = 0.947. There is some discussion in the literature on alternative methods for choosing the scale factor, but the above procedure is widely used.²¹

The appropriate choice of theoretical method must also give accurate relative energies for a family of related phenolic compounds and should give a reasonable value for the BDE of phenol itself. Table 3 shows the total energy and (scaled) ZPE obtained for phenol and the phenoxy radical obtained using the B3LYP functional with four different basis sets. The ZPE is the same in all four basis sets since it is obtained from the

Table 3. Total and Relative Energies from the DFT Calculation with Four Different Basis Sets^a

basis set and ZPE	phenol	phenoxy	ΔH_{298}^0 ^b
6-31G	-307.38656	-306.74867	79.51
6-31G(d)	-307.46415	-306.82693	77.13
6-31G(d,p)	-307.47769	-306.83463	82.75
6-31G(p')	-307.40932	-306.76053	86.35
ZPE	0.10696	0.09309	
ZPE(s)	0.10129	0.08815	
ZPE(s), corr	0.10804	0.09474	

^a Total and ZPE energies in hartree, ΔH_{298}^0 values in kcal/mol. ZPE(s) = scaled ZPE by 0.947, ZPE(s), corr = scaled ZPE with enthalpy corrections (see text). H-atom total energy = -0.50027 hartree in all four basis sets and the correction $^{3/2}RT = 0.00094$ hartree (see text). ^b $\Delta H_{298}^0 = \text{BDE}(\text{PhO}-\text{H})^{\text{gas}}$; "best" experimental value = 87.3 ± 1.5 kcal/mol, see refs 10, 11, and 22.

AM1 frequency calculation at the AM1 optimized geometry. The H atom total energy is also the same in all four basis sets since the polarization functions do not contribute to the DFT energy. The thermal corrections contain the scaled ZPE + $^{3/2}RT$ (translation) + $^{3/2}RT$ (rotation) plus a small amount (vibrational excitation) for phenol and phenoxy, and add RT to convert from energy to enthalpy ($H = E + PV = E + RT$). For the H atom, adding $^{3/2}RT$ (translation) + RT (enthalpy conversion) completes the data entries to Table 3.

The final column of Table 3 shows the values of ΔH_{298}^0 for the reaction $\text{PhOH} \rightarrow \text{PhO} + \text{H}$, obtained using the zero-point and temperature corrected values as described above. The values of ΔH_{298}^0 are directly comparable to experimental bond dissociation enthalpies (BDE's). The "best" experimental value for $\text{BDE}(\text{PhO}-\text{H})^{\text{gas}}$ is 87.3 ± 1.5 kcal/mol.^{10,11,22} This is the mean of experimental measurements by photoacoustic calorimetry in five solvents having very different hydrogen bond accepting properties (range 86.2–88.3 kcal/mol).¹⁰ This value agrees very well with a recommended value of 87 kcal/mol based on various measurements in the gas phase (range 85.1–88.3 kcal/mol).^{10,24}

The 6-31G basis set gives a value for $\text{BDE}(\text{PhO}-\text{H})^{\text{gas}}$ that is about 8 kcal/mol lower than the experimental value of 87.3 kcal/mol. Adding d -polarization functions on the heavy (C and O) atoms makes the situation slightly worse (6-31G(d) basis set, 77.13 kcal/mol), whereas adding polarization functions on both heavy atoms and hydrogen improves the BDE (6-31G(d,p) basis set, 82.75 kcal/mol). However, the calculation using the 6-31G(d,p) basis set will become rather costly for larger systems, and the result is still almost 5 kcal/mol below the "best" experimental value. Selectively adding polarization functions only on hydrogen seems to be optimum from the point of view of both cost (only three extra functions per H atom) and BDE, giving a value of 86.35 kcal/mol, which is within 1 kcal/mol of the experimental value.

Many of the compounds reported in this paper have methyl, methoxy, or amino groups that are subject to low-frequency torsion or bending modes. These low frequency modes are problematic since they contributed strongly to the vibrational function and hence can significantly affect the vibrational contribution to the enthalpy. They are difficult to describe accurately at any level of theory, and there is no reason to expect them to be particularly well described by our scaled AM1

(22) For a compilation of other solution-phase measurements that have been used to calculate $\text{BDE}(\text{PhO}-\text{H})^{\text{gas}}$ (range 84.0–91.6 kcal/mol), see ref 10. Only two values fall within ± 1.5 kcal/mol of the PAC value, viz., ≤ 88.2 kcal/mol^{8b} and 88.3 kcal/mol.²³

(23) Mahoney, L. R.; DaRooge, M. A. *J. Am. Chem. Soc.* **1975**, *97*, 4722–4731.

(24) Arends, I. W. C. E.; Louw, R.; Mulder, P. *J. Phys. Chem.* **1993**, *97*, 7914–7925.

(19) Hagen, K.; Hedberg, K. *J. Chem. Phys.* **1973**, *59*, 158–162.

(20) Bist, H. D.; Brand, J. C. D.; Williams, D. R. *J. Mol. Spectrosc.* **1967**, *24*, 402–412.

(21) Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian Inc.: Pittsburgh, PA, 1995.

Table 4. Comparison of Calculations with Experiment for [BDE(PhO–H, **1**)^{gas} – BDE(O–H in 2,6-dimethyl-4-methoxyphenol, **21**)^{gas} = $\Delta(\Delta H_{298}^0)$ in kcal/mol

$\Delta(\Delta H_{298}^0)$	basis set				expt
	6-31G	6-31G(d)	6-31G(d,p)	6-31G(p')	
	8.3	7.9	9.2	8.5	10.1

frequencies. It therefore seemed prudent to omit this part of the enthalpy correction. Using electronic energies and the scaled zero-point energies (Table 3), an estimate of the value of ΔH_{298}^0 is then obtained by adding the electronic energy + scaled ZPE (for products – reactants) and adding $5/2RT$ to the total, thus allowing for everything but vibrational excitation contributions to the enthalpy. This results in a value of 86.46 kcal/mol for the 6-31G(p') basis, i.e., the difference between the more rigorous treatment and this approximate treatment is very small (0.11 kcal/mol). This last approach was therefore used in all further calculations.

As mentioned above, a slightly different value of ΔH_{298}^0 would result if optimized geometries were taken from the B3LYP/6-31G(p') basis set. Using the B3LYP/6-31G(p') geometries from Table 2 gave –307.41088 and –306.76308 hartrees for phenol and phenoxyl, respectively. Using these values and the scaled, thermally corrected ZPE from Table 3 leads to $\Delta H_{298}^0 = 85.69$ kcal/mol. Thus we have introduced a systematic error of $86.35 - 85.69 = 0.66$ kcal/mol into the calculations if AM1 geometries are used. However, the computational advantage is substantial when AM1 geometries and especially frequencies are used, so we shall use that method. The geometry/frequency/method/basis can then be labeled as AM1/AM1//B3LYP/6-31G(p').

Because the 6-31G(p') basis set is unorthodox, we performed one additional test and examined the energy lowering of the gas-phase O–H BDE of a well-studied substituted phenol relative to phenol. The phenol chosen was 2,6-dimethyl-4-methoxyphenol, **21**, and the decrease in ΔH_{298}^0 relative to phenol was calculated with the four different basis sets. This compound has been shown to have an O–H BDE of 77.2 kcal/mol by photoacoustic calorimetry,¹¹ which represents a decrease in O–H BDE of 10.1 kcal/mol relative to phenol *utilizing the same experimental technique*.^{11,25} This substantial decrease in O–H BDE provides a useful “reality check” for our calculations. Table 4 gives the calculated lowering in the O–H BDE relative to phenol. The four calculations differ from the experimental value by an average of 1.6 kcal/mol, but they show good consistency, with a spread of values of only ± 0.7 kcal/mol. For the reasons given below, the 6-31G(p') basis was used in all further calculations, but for larger compounds containing several rings, the smaller 6-31G basis should provide fairly reliable differences in O–H BDE's.

One potentially important factor for the O–H BDE's of ring-substituted phenols is the degree of planarity of the O–H bond relative to the phenyl ring. For phenol (**1**) the double minimum potential for rotation of the OH group has the minima with the O–H bond coplanar with the aromatic ring and the maxima with the O–H bond perpendicular to the ring. The DFT-calculated, ZPE-corrected rotation barrier was found to be 3.57 kcal/mol, in excellent agreement with experimental measurements and theoretical calculations.²⁶ When a substituent is located in the *ortho* position, there will frequently be a repulsive (steric) interaction between the OH group and the substituent. When both *ortho* positions are substituted, this must destabilize

(25) The ESR equilibrium method gave an O–H BDE of 77.6 kcal/mol for 2,6-dimethyl-4-methoxyphenol.⁷

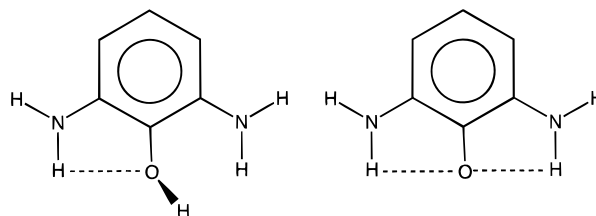


Figure 1. *o,o*-Diaminophenol and its phenoxyl radical.

the parent molecule and, in extreme cases, might even force the O–H bond out of plane. However, it should be noted that even two bulky *tert*-butyl groups do not manage to achieve this. That is, in 2,6-di-*tert*-butyl-4-substituted phenols the O–H group remains in the plane of the aromatic ring.²⁷ Furthermore, in 2-*tert*-butylphenols and in 2-*tert*-butyl-6-methylphenols the two isomers having the OH group pointing toward and away from the *tert*-butyl group can be observed by infrared spectroscopy both in solution²⁸ and in the gas phase.²⁹

A methoxy substituent on an aromatic ring also has a similar double-minimum potential with minima occurring when the O–CH₃ bond is coplanar with the ring. The larger size of the OCH₃ group relative to the OH group means that it can be much more readily forced out of the aromatic ring plane by adjacent alkyl groups. Thus, for a *p*-methoxy phenol containing *two meta*-methyl substituents the O–CH₃ bond is forced out-of-plane^{4a,4b} which destabilizes the phenol and, more importantly, destabilizes the derived radical (since the oxygen atom of the methoxy group will become much less effective at π -conjugation with the unpaired electron).^{4a,4b}

Finally, when *ortho* substituents contain oxygen or nitrogen, hydrogen bonding can occur between the phenolic H atom and the heteroatom of the substituent. This will stabilize the phenol and hence cause an increase in the O–H BDE, cf., *vide infra*, the O–H BDE's for phenol (**1**), for *o*-methoxyphenol with internal hydrogen bonding (**15**; toward) and without such bonding (**14**; away), and for *p*-methoxyphenol (**16**). Alternatively, if the substituent(s) can act as hydrogen bond donors to the phenolic oxygen atom (e.g., *o*-NH₂ groups) the corresponding phenoxyl radical may be stabilized relative to the phenol (see Figure 1) with a consequent decrease in its O–H BDE. Examination of calculated O–H BDE's with the foregoing ideas in mind helps to explain the observed trends as does the additivity scheme described below.

Table 5 gives calculated BDE(ArO–H)^{gas} values for phenols **1–35**. These data are corrected for (scaled) zero-point energy differences between the parent molecules and radicals using AM1 ZPE's, as described earlier, and thermally corrected to obtain enthalpy values. These ZPE corrections range from 7.9 to 8.3 kcal/mol. Formation of the radical involves loss of an O–H stretch, Ar–O–H bend, and ArOH torsion in the parent, with some strengthening of the Ar–O bond in the radical. The small range of ZPE variations shows that the calculation of substituent effects will not be highly sensitive to the ZPE corrections, although using an average value of 8.1 kcal/mol would have led to some obscuring of the additivity effect of multiple substituents. For phenols (**1–23** and **31–35**), chro-

(26) Experimental values are 3.4 ± 0.1 kcal/mol; see: Forest, H.; Dailey, B. P. *J. Chem. Phys.* **1966**, *45*, 1736–1746. Quade, C. R. *J. Chem. Phys.* **1968**, *48*, 5490–5493. Mathier, E.; Welti, D.; Bauder, A.; Gunthard, H. J. *Mol. Spectrosc.* **1971**, *37*, 63–76. For theoretical values using MP2 methods, 3.35 kcal/mol, see: Kim, K.; Jordan, K. D. *Chem. Phys. Lett.* **1994**, *218*, 261–269. For theoretical values using DFT methods, 3.21 kcal/mol, see: Costa Cabral, B. J.; Fonseca, R. G. B.; Simoes, J. A. M. *Chem. Phys. Lett.* **1996**, *258*, 436–444.

(27) Ingold, K. U. *Can. J. Chem.* **1960**, *38*, 1092–1098.

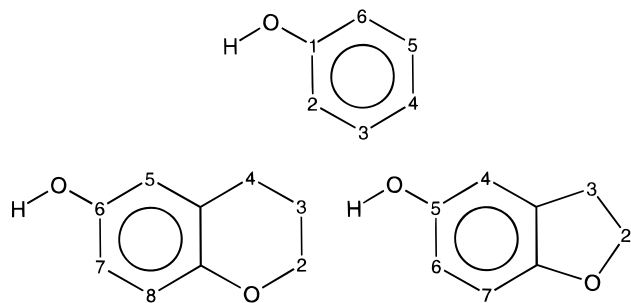
(28) Ingold, K. U.; Taylor, D. R. *Can. J. Chem.* **1961**, *39*, 471–480. Ingold, K. U.; Taylor, D. R. *Can. J. Chem.* **1961**, *39*, 481–487.

(29) Ingold, K. U. *Can. J. Chem.* **1962**, *40*, 111–121.

Table 5. Calculated Bond Dissociation Enthalpies (BDE's) for Some Phenols

structure (OH orientation)	substituents					BDE (gas) (kcal/mol)	Δ (DFT) (kcal/mol)	Δ (add.) (kcal/mol)
	ortho	meta	para	meta	ortho			
1	H	H	H	H	H	86.46	0.00	
2 (away)	Me	H	H	H	H	84.86	-1.60	<i>a</i>
3 (toward)	Me	H	H	H	H	83.80	-2.66	<i>a</i>
4 (away)	H	Me	H	H	H	85.22	-1.24	-0.52
5 (toward)	H	Me	H	H	H	86.13	-0.33	-0.52
6	H	H	Me	H	H	84.54	-1.92	<i>a</i>
7	Me	H	H	H	Me	82.25	-4.21	-4.26
8 (away)	Me	Me	H	H	H	83.95	-2.51	-2.10
9 (toward)	Me	Me	H	H	H	82.52	-3.94	-3.16
10	H	Me	H	Me	H	85.97	-0.49	-1.04
11 (away) ^b	Me	H	H	Me	H	84.47	-1.99	-2.10
12 (toward) ^b	Me	H	H	Me	H	83.48	-2.98	-3.06
13	Me	H	Me	H	Me	80.40	-6.06	-6.18
14 (away)	OMe	H	H	H	H	82.11	-4.35	
15 (toward)	OMe	H	H	H	H	87.80	+1.34	
16	H	H	OMe	H	H	82.01	-4.45	<i>a</i>
17	OMe	H	H	H	OMe	82.41	-4.05	
18 (away)	Me	H	OMe	H	H	80.44	-6.02	-6.05
19 (toward)	Me	H	OMe	H	H	79.40	-7.06	-7.11
20	H	Me	OMe	H	H	81.96	-4.50	-4.95
21	Me	H	OMe	H	Me	78.01	-8.45	-8.60
22	H	Me	OMe	Me	H	85.08	-1.38	-5.45
23	Me	Me	OMe	Me	Me	79.37	-7.09	-9.71
24	H	MeChr	OChr	H	H	81.42	-5.04	<i>a</i>
25 ^c	H	MeChr	OChr	Me	H	81.43	-5.03	-5.54
26 (away) ^d	Me	MeChr	OChr	Me	H	79.35	-7.11	-7.14
27 (away) ^e	H	MeChr	OChr	Me	Me	79.57	-6.89	-7.14
28 ^f	Me	MeChr	OChr	Me	Me	75.78	-10.68	-9.80
29	H	Me-Fur	OFur	H	H	80.24	-6.22	<i>a</i>
30	Me	Me-Fur	OFur	Me	Me	75.14	-11.32	-10.96
31 (away)	NH ₂	H	H	H	H	73.81	-12.65	
32 (toward)	NH ₂	H	H	H	H	71.95	-14.51	
33	H	H	NH ₂	H	H	77.65	-8.81	
34	NH ₂	H	H	H	NH ₂	64.18	-22.28	
35	NH ₂	H	OMe	H	NH ₂	64.67	-21.79	

^a Value used to assign substituent constant for this position and functional group. ^b With respect to the *o*-methyl group. ^c Model for δ -tocopherol. ^d Model for β -tocopherol. ^e Model for γ -tocopherol. ^f Model for α -tocopherol.

**Figure 2.** Ring numbering for phenols, chromanols and dihydrobenzofuranols.

manols (**24–28**), and dihydrobenzofuranols (**29, 30**) the standard ring numbering notation for substituents is shown in Figure 2. For simple phenols the first column labeled “*ortho*” corresponds to the 2-position, “*meta*” to the 3-position, and so forth. For the chromanol ring system, the first (*ortho*) column refers to the 5-position, the last (*ortho*) column is the 7-position, and the oxygen atom of the saturated ring occurs *para* to the phenolic OH. A similar scheme is used for the dihydrobenzofuranol ring system.

For phenols with single *ortho* and/or single *meta* substituents it is necessary to distinguish between the *away* and *toward* conformations of the OH group relative to the substituent(s) (see Figure 3). These are true minima on the calculated potential surface for the OH torsional motion (separated in phenol, for example, by a calculated barrier of 3.57 kcal/mol, *vide supra*). At room temperature there will be an equilibrium between, for example, the *o*-methylphenol structures **2** (away) and **3** (toward).

The away conformer has the lower (ZPE-corrected) enthalpy in the DFT calculation by 1.06 kcal/mol. This may be compared with infrared experimental measurements from which the away conformer of *o*-methylphenol was estimated³⁰ to be more stable than the toward conformer both in solution ($\Delta H \approx \Delta G \approx 0.5_1$ kcal/mol, away isomer = 70.5%, toward isomer = 29.5% at 24 °C)^{28,31} and in the vapor phase ($\Delta H = 0.3_5$ kcal/mol).²⁹ Loss of the phenolic H atom in the radical means that there is no longer any distinction between away and toward so the effect is only on the parent phenol.

Table 5 gives the calculated gas-phase O–H bond dissociation enthalpy (at 298.15 K) for phenols **1–35**. In order to use these data to determine whether an additivity scheme holds, one must be careful to note conformational differences between isomers that might be treated as identical at a lower level of theory. It is possible to be trapped in local minima if a poor starting point is chosen for the geometry optimization in a complex structure. To avoid this, all optimized structures were scanned visually by using molecular drawing packages to ensure reasonable structures. In difficult cases, multiple starting points were used to ensure that optimum structures were found.

For example, in the away conformer of *o*-methylphenol, **2**, the O–H bond is 1.60 kcal/mol weaker than the O–H bond in

(30) These estimates are based on measurements of the ratio of toward and away conformers (with respect to the *tert*-butyl group) in 2-*tert*-butyl-4-methylphenol ($\Delta G^{\text{CCl}_4} = 1.5_7$ kcal/mol,²⁸ $\Delta H^{\text{vapor}} = 1.6_1$ kcal/mol.²⁹) and 2-*tert*-butyl-6-methylphenol ($\Delta G^{\text{CCl}_4} = 1.0_6$ kcal/mol,²⁸ $\Delta H^{\text{vapor}} = 1.2_6$ kcal/mol.²⁹)

(31) There is some minor uncertainty regarding the difference in energy between **2** and **3**, viz., 1.1 kcal/mol (present calculations), 0.5₁ kcal/mol,^{28,30} and 0.3₅ kcal/mol.^{29,30}

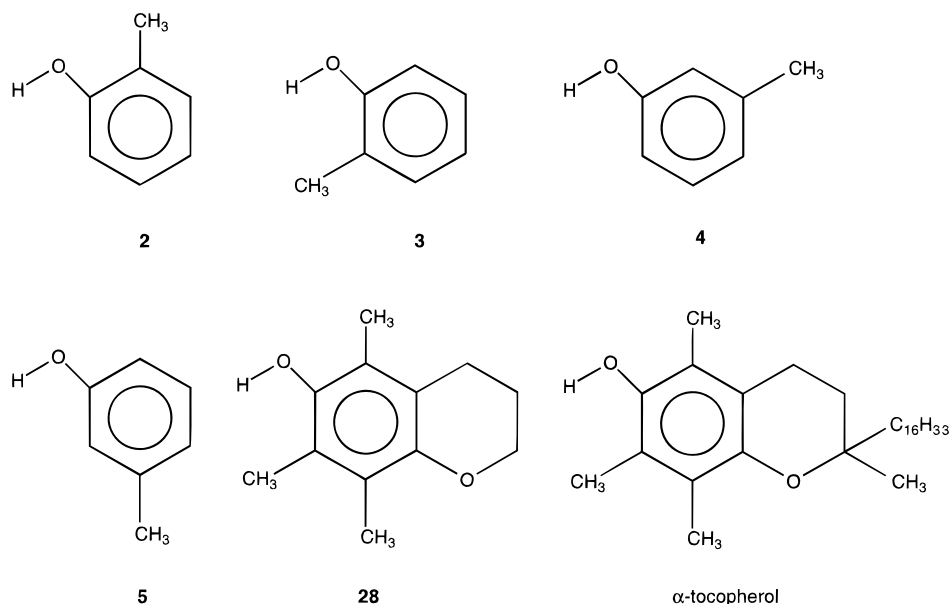


Figure 3. Structures of selected phenols.

phenol, whereas in the toward conformer, **3**, the O–H bond is 2.66 kcal/mol weaker than in phenol (see Figure 3).³¹ This is readily understandable because **3** is more destabilized than **2** due to steric repulsion. In *o,o*-dimethylphenol, **7**, perfect additivity of both groups would imply an O–H bond weakening relative to phenol of $1.60 + 2.66 = 4.26$ kcal/mol, viz., an O–H BDE of 82.2 kcal/mol in excellent agreement with the directly calculated BDE of 82.25 kcal/mol. Experimental measurements on the bond weakening effect of one *o*-methyl group have yielded 1.7 kcal/mol^{8c} and those on the combined bond weakening effect of two *o*-methyl groups have yielded 4.3 kcal/mol.^{8c,11} This last value is in excellent agreement with the DFT value.

The O–H bond weakening effect of a *m*-methyl group would be expected to be the same for the away, **4**, and toward, **5**, conformers (see Figure 3), but our calculations yield values of 1.24 and 0.33 kcal/mol, respectively (see Table 5). The O–H BDE is calculated to be only 0.49 kcal/mol weaker in *m,m*-dimethylphenol, **10**, than in phenol, a value which certainly is not the sum of the two effects taken independently. The choice of a best value is therefore uncertain, but using all data would give $(1.24 + 0.33 + 0.25 + 0.25)/4 = 0.52$ kcal/mol per *m*-methyl substituent which is in reasonable agreement with an experimental estimate of 0.4 kcal/mol.³²

The O–H BDE is calculated to be 1.92 kcal/mol weaker in *p*-methylphenol, **6**, than in phenol. This bond weakening effect is somewhat greater than the 1.6 kcal/mol of an *o*-methyl group in the away conformer, **2**. Experimental measurements have yielded $\text{BDE}(\text{PhO}-\text{H}) - \text{BDE}(4\text{-CH}_3\text{C}_6\text{H}_4\text{O}-\text{H}) = 2.1$,^{8b} 1.1,^{8c} and 2.2^{8d} kcal/mol.³³

The remaining phenols, **7–13**, have methyl substituents at various other places on the aromatic ring. In all cases except one, the difference between the directly calculated O–H BDE's and those estimated assuming additivity is 0.6 kcal/mol or less whereas in **9** it is 0.8 kcal/mol.³⁴ The O–H BDE for 2,4,6-trimethylphenol, **13**, has been measured experimentally as 81.8

kcal/mol,¹¹ corresponding to a total bond weakening by the three methyl groups of 5.5 kcal/mol relative to phenol, a value that compares quite well with values of 6.06 kcal/mol from the DFT calculations and 6.18 kcal/mol from group additivity.

The effect of adding a methoxy group to the aromatic ring and the combined effect of methoxy and methyl substituents is shown in phenols **14–23** (Table 3). A *p*-methoxy group, **16**, weakens the O–H bond by 4.45 kcal/mol, so this was taken as the group effect for a coplanar methoxy group although experimentally the bond weakening effect of this group has been found to be somewhat larger, viz., 5.3,^{8c} 5.6,^{8b,11} 5.7,^{8d} and 9.1⁹ kcal/mol. For *o*-methoxyphenol the toward conformer, **15**, is calculated to be 5.69 kcal/mol more stable than the away conformer, **14**, because of internal hydrogen bonding in **15**. Indeed, the O–H bond is actually 1.34 kcal/mol *stronger* in **15** (toward) than in phenol, **1**. However, the O–H bond in **14** (away) is calculated to be 4.35 kcal/mol weaker than that in phenol. Thus, were it not for internal hydrogen bonding the effect of an *o*-methoxy group would be essentially the same as that of a *p*-methoxy group. For *o,o*-dimethoxyphenol, **17**, in which internal hydrogen bonding must occur, our calculations indicate that one OMe group points away from the OH group (the hydrogen bond accepting OMe) and one OMe group points toward the OH group. However, in the corresponding radical both OMe groups are calculated to point away from the phenoxyl radical's oxygen atom. This change in conformation presumably accounts for the calculated O–H BDE for **17** being 82.41 kcal/mol whereas strict additivity would imply $87.80 - 4.35 = 83.45$ kcal/mol.

The directly calculated $\text{BDE}(\text{ArOH})^{\text{gas}}$ and the values obtained by additivity with the constants for methyl substituents derived above are in good agreement for phenols **18–21**. However, this is not the case for phenols **22** and **23** for which the calculated structures show that the two *meta* groups force the *p*-methoxy group out of plane to create an Ar–O–CH₃ dihedral angle of 84°, which almost eliminates the normal substituent effect of this group. These calculated angles are in excellent agreement with the results of an X-ray structural study

(32) $\text{BDE}(\text{PhO}-\text{H}) - \text{BDE}(3\text{-CH}_3\text{C}_6\text{H}_4\text{O}-\text{H}) = 0.44$ kcal/mol^{8c} and $\text{BDE}(\text{PhO}-\text{H}) - \text{BDE}(3,5\text{-(CH}_3)_2\text{C}_6\text{H}_3\text{O}-\text{H}) = 0.74$ kcal/mol,^{8c} mean of 0.88 and $0.74 \approx 0.8$ kcal/mol.

(33) $\text{BDE}(\text{PhO}-\text{H}) - \text{BDE}(4\text{-(CH}_3)_3\text{CC}_6\text{H}_4\text{O}-\text{H}) = 1.9$ kcal/mol.⁹ The bond weakening effect is expected to be similar for the 4-CH₃ and 4-(CH₃)₃C groups.

(34) Infrared measurements on the toward and away conformers (w.r.t. *tert*-butyl) of 2-*tert*-butyl-5,6-dimethylphenol yield $\Delta G^{\text{CCl}_4} = 0.8_0$ kcal/mol,²⁸ $\Delta H^{\text{vapor}} = 0.9_0$ kcal/mol,²⁹ from which the steric destabilization in 2,3-dimethylphenol when the O–H group points toward the two methyl groups was estimated to be 0.7–²⁸ and 0.7₁ kcal/mol.²⁹

of **23**, which showed a dihedral angle of 88.6° .^{4a,b} This X-ray structure was originally obtained to confirm a tentative explanation as to why such a seemingly good model for α -tocopherol was such a relatively poor antioxidant.^{4a,b}

In the four tocopherols that together constitute vitamin E nature has made use of the chromanol structure instead of using phenols substituted with two *m*-methyl groups and a *p*-methoxy group. In this way, the tocopherols retain most of the radical-stabilizing effect of the *p*-alkoxy group while gaining the radical-stabilizing effect of two *m*-alkyl groups (**25** is a model for δ -tocopherol), two *m*- and one *o*-alkyl groups (**26** and **27** are models for β - and γ -tocopherol, respectively), and four alkyl groups (**28** is a model for α -tocopherol, see Figure 3). The effect of the chromanol structure on calculated O–H BDE's is given for **24–28** in Table 3 (which indicates that one ring carbon is attached *meta* and the ring oxygen is attached *para* to the hydroxyl group). Compound **24** shows that the effect of the chromanol ring is to reduce BDE(ArOH)^{gas} by 5.04 kcal/mol relative to phenol, which may be compared with the sum of 0.4 kcal/mol from one *m*-methyl group³² plus 5.3^{8c} or 5.6^{8b,11} kcal/mol from a *p*-alkoxy group, i.e., 5.7–6.0 kcal/mol.

Assigning 5.04 kcal/mol as the O–H bond-weakening effect of the chromanol group and the values for methyl substituents given earlier shows that additivity and directly calculated O–H BDE's are in good agreement for phenols **25–27**. For the α -tocopherol model, **28**, we obtain the DFT value for O–H bond weakening of 10.68 kcal/mol while the additive value is 9.8 kcal/mol, still in reasonably good agreement. The O–H BDE in α -tocopherol has been measured by photoacoustic calorimetry to be 77.3 kcal/mol,¹¹ i.e., 10.0 kcal/mol lower than the O–H bond strength for phenol measured by the same technique.³⁵

Appropriately substituted dihydrobenzofuranols (see Figure 2) have been shown to be more effective antioxidants than the chromanols. This is because the five-membered ring in the dihydrobenzofuran system provides a better orientation of the ring oxygen atom's lone pair(s) for stabilization of the corresponding phenoxyl radical than is the case for the chromanols (Ar–O–C dihedral angles measured by X-ray analyses are ca. 6° for the former and ca. $17–19^\circ$ for the latter).^{4b} Comparison of the dihydrobenzofuranols **29** and **30** with the corresponding chromanols **24** and **28** shows that the smaller ring reduces the O–H bond strength by ca. 1.0 kcal/mol relative to the larger ring (range 0.7–1.3 kcal/mol). These calculated O–H BDE's lend further support to the original stereoelectronic explanation for the high antioxidant activity of α -tocopherol^{4a} and are consistent with the fact that the dihydrobenzofuranols are ca. 50% better antioxidants *in vitro*^{4b} and, in one test, would appear to have ca. 50% more vitamin E activity *in vivo*.^{4c}

An alternative approach to the effect on BDE(ArO–H) values of multiple substitution on the aromatic ring has been developed by Jonsson *et al.*³⁷ An empirical equation that relates differences in phenolic O–H bond strengths to the sum of the Brown σ^+ constants for all the ring substituents, viz.,

$$\Delta\text{BDE}(\text{ArO}-\text{H})/\text{kcal/mol} = 7.14[\sum(\sigma^+_{\text{o}} + \sigma^+_{\text{m}} + \sigma^+_{\text{p}})] - 0.47$$

gave a remarkably good correlation ($r^2 = 0.96$).^{37,38} The BDE(ArO–H) values used had been obtained by a variety of

(35) The ESR equilibrium method has yielded O–H BDE values in α -tocopherol of 78.9⁷ and 78.6³⁶ kcal/mol.

(36) Jackson, R. A.; Hosseini, K. M. *J. Chem. Soc., Chem. Commun.* **1992**, 967–968.

(37) Jonsson, M.; Lind, J.; Eriksen, T. E.; Merényi, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1567–1568.

experimental techniques using water as the solvent and were conditional upon the following relationship, $\sigma^+_{\text{o}} = 0.66 \sigma^+_{\text{p}}$. The factor of 0.66 was based on the different effects of *o*- and *p*-methoxy groups on BDE(ArO–H)^{37,39} and would be less affected by internal hydrogen bonding of the *o*-methoxyphenols in aqueous systems than would be the case for measurements made in benzene or the gas phase. This “perturbation” will be absent in *o*-methylphenols and, indeed, *o*-methyl groups (in the away conformation) can be estimated to have 82–87% of the effect of *p*-methyl on O–H BDE's.³⁹

Novel Phenols

Both our calculations and experimental data show that when an O–H group and an *o*-methyl group are in the toward configuration, the phenol is destabilized relative to the phenoxyl radical with a consequent decrease in the O–H BDE. The steric repulsion exerted by two *o*-methyl groups is insufficient to force the O–H bond out of the plane of the aromatic ring, and this is also true even for two *o*-*tert*-butyl groups (*vide supra*). Apparently, in these compounds the phenolic hydrogen atom can lie in-plane because it “tucks” itself between two out-of-plane H atoms (of *o*-methyl) or CH₃ groups (of *o*-*tert*-butyl) while the third atom or group which is furthest removed from the O–H group lies more or less in the aromatic ring plane. It occurred to us that such a “neat” in-plane “fit” of the O–H group into the “cleft” within an *o*-alkyl group might not be possible with an *o*-amino group, NH₂. That is, although the NH₂ group in *o*-aminophenol is nonplanar it will, nevertheless, interact sterically with the OH group. Thus, two *o*-NH₂ groups might cause the phenolic O–H bond to twist out of the aromatic plane with a consequent weakening of this bond. Furthermore, the corresponding phenoxyl radical is expected to be stabilized by internal hydrogen bonding from the two *o*-NH₂ groups to the oxygen atom (see Figure 1).

Our calculations (Table 5) indicate that a single NH₂ group in the *ortho* position lowers the O–H BDE by 12.65 kcal/mol in **31** (away) and by 14.51 kcal/mol in **32** (toward) conformations while a *p*-amino group, **33**, has an O–H bond-weakening effect of 8.81 kcal/mol. The calculated O–H bond-weakening effect of the *p*-NH₂ group is considerably smaller than experimental estimates of this quantity, viz., 12.7^{8b} and 12.6^{8c} kcal/mol. Nevertheless, both calculation and experiment indicate that NH₂ groups have much larger effects on O–H BDE's than methoxy groups. In *o,o*-diaminophenol, **34**, the O–H BDE is

(38) A very similar equation, viz., $\Delta\text{BDE}(\text{ArO}-\text{H})/\text{kcal/mol} = 7.32 [\sum(\sigma^+_{\text{o}} + \sigma^+_{\text{m}} + \sigma^+_{\text{p}})] - 0.64$ ($r^2 = 0.97$), correlates BDE's measured only by photoacoustic calorimetry for several mono *para*- and *meta*-substituted phenols, two 2,6-dimethyl-4-substituted phenols, and 2,4-di-*tert*-butylphenol, again with the proviso that $\sigma^+_{\text{o}} = 0.66 \sigma^+_{\text{p}}$.¹¹ In contrast to the work of Jonsson *et al.*,³⁷ no *o*-methoxy substituted phenols were examined. Taking $\sigma^+_{\text{o}} = \sigma^+_{\text{p}}$ yields $\Delta\text{BDE}(\text{ArO}-\text{H})/\text{kcal/mol} = 6.68 [\sum(\sigma^+_{\text{o}} + \sigma^+_{\text{m}} + \sigma^+_{\text{p}})] - 0.40$ with $r^2 = 0.99$.

(39) The one-electron reduction potentials of various *o*- and *p*-substituted phenoxyl radicals also yield $\sigma^+_{\text{o}}(\text{MeO}) \approx 0.66 \sigma^+_{\text{p}}(\text{MeO})$.^{37,40} However, comparison of the reduction potentials for the radicals from phenol (0.79 V), 4-methylphenol (0.68 V), and 2,4,6-trimethylphenol (0.49 V) would suggest that $\sigma^+_{\text{o}}(\text{Me}) = [(0.79 - 0.49) - (0.79 - 0.68)]/2(0.79 - 0.68) \sigma^+_{\text{p}}(\text{Me})$, i.e., $\sigma^+_{\text{o}}(\text{Me}) = 0.86 \sigma^+_{\text{p}}(\text{Me})$. A comprehensive tabulation of σ constants⁴¹ gives $\sigma^+_{\text{p}}(\text{Me}) = -0.31$ and $\sigma^+_{\text{o}}(\text{Me}) = -0.27$, i.e., $\sigma^+_{\text{o}} = 0.87 \sigma^+_{\text{p}}$. Our calculations give O–H bond weakening effects for **2** and **6** of 1.6 and 1.9 kcal/mol, respectively (Table 5), corresponding to an *o*-methyl (away)/*p*-methyl ratio of 0.84. Similarly, kinetic data for reaction 1 (which correlates with σ^+)⁴² yield $\sigma^+_{\text{o}}(\text{Me}) \approx 0.82 \sigma^+_{\text{p}}(\text{Me})$ by comparing the rate constants for *meta*- and *para*-substituted phenols⁴² with those for 2,6-dimethyl-4-substituted phenols.⁴³

(40) Jonsson, M.; Lind, J.; Reiterberger, T.; Eriksen, T. E.; Merényi, G. *J. Phys. Chem.* **1993**, *97*, 8229–8233.

(41) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

(42) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 1744–1751.

(43) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 2800–2806.

calculated to be reduced by an astounding 22.28 kcal/mol, which is only slightly lower than the value calculated by simple additivity, i.e., 12.65 (away) + 14.51 (toward) = 27.16 cal/mol. The absence of strict additivity is not surprising when the phenol is subject to such large perturbations. The optimized AM1 conformations of **34** (see Figure 1) show that the two hydrogen atoms on each of the two amino groups are slightly out of line with the aromatic ring plane and that the O–H bond is nearly perpendicular to this plane (Ar–O–H dihedral angle = 71°). In the corresponding diaminophenoxy radical the amino groups become strictly planar and coplanar with the aromatic ring. Thus, there is considerable destabilization of the parent phenol and strong stabilization of the phenoxy radical, which causes the very large decrease in the O–H BDE. We estimate that the actual O–H BDE in 2,6-diaminophenol, **34**, would be ca. 65 kcal/mol, which is far below that in α -tocopherol, viz., 77.3–78.9 kcal/mol.^{7,11,36} We note, however, that our calculations on the aminophenols should undergo further basis set testing, including geometry optimization, to make sure that these NH₂ group effects are real.

The addition to **34** of further substituents, such as the *p*-methoxy group, **35**, leads to no further O–H bond weakening. Evidently, the interaction of the two *o*-amino groups with the OH group and the aromatic ring stabilizes the phenoxy radical to such an extent that no role is left for other groups (such as *p*-methoxy) that normally add conjugative stabilization.

In connection with the foregoing, it should be noted that aminophenols are not employed commercially as antioxidants (as far as we are aware). The reason is that many of these phenols are quite unstable in air, undergoing a fairly rapid direct reaction with oxygen.⁴⁴

Conclusions

We have presented a density functional method of calculation that appears to be capable of giving reasonably accurate values for gas-phase phenolic O–H bond dissociation enthalpies. The method was used to determine the O–H bond weakening effects of methyl and methoxy substituents, and it was confirmed that

(44) For example, the analogue of **28** in which the oxygen atom in the ring was replaced by an NH group was found to be unstable in air even in the crystalline state.^{4b}

simple additivity rules hold rather well (except for a few anomalous cases that were predictable).⁴⁵

The calculations were extended to include fused 6- and 5-membered oxygenated rings, the chromanol (related to vitamin E) and dihydrobenzofuranol systems, respectively. The results were internally self-consistent, and simple additivity rules were again useful. The direct DFT calculation of the O–H bond weakening in an α -tocopherol model compound gave 10.7 kcal/mol, the bond weakening following the additivity rules gave 9.8 kcal/mol, and both of these values are fairly close to the experimental value of 10.0 kcal/mol. The parameters derived here are therefore useful for molecules of biological significance.

Amino groups in the *ortho* position have a remarkably large O–H bond weakening effect. These compounds, and substituted amines derived from these compounds, may represent a new line of investigation in the search for more effective antioxidants.

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(45) Following submission of the present paper, a publication appeared describing the calculation of O–H BDE's for phenol and a large number of *para*-substituted phenols using DFT.⁴⁶ For phenol the O–H BDE was calculated to be 75.1 (BLYP/6-31G*), 87.8 (JMW/DN), and 89.4 (JMW/DND) kcal/mol. There were three *para*-substituted phenols in this study which we had also examined. At the BLYP/6-31G* and JMW/DN levels of theory BDE(PhO–H) – BDE(4-XC₆H₄O–H) differences were 1.9 and 2.9 (X = CH₃), 6.0 and 7.1 (X = CH₃O), and 9.1 and 12 (X = NH₂) kcal/mol, respectively. Following acceptance of the present paper, a very important publication appeared⁴⁷ that describes an extension of the ESR equilibrium method for measuring differences in ArO–H BDE's^{5,7} to phenols yielding transient phenoxy radicals. The agreement with our calculations is very gratifying, e.g.,⁴⁷ (PhO–H)BDE = 88.3 ± 0.8 kcal/mol, and Δ BDE/kcal/mol for phenol substituted with two *ortho*, two *meta*, or a *para* substituent are as follows: for Me, –3.5, –1.0, and –1.7; for Me₃C, –4.8, –1.0, and –1.9; and for MeO, –3.9, –0.9, and –4.4, respectively.

(46) Wu, Y.-D.; Lai, D. K. W. *J. Org. Chem.* **1996**, *61*, 7904–7910.

(47) Lucarini, M.; Pedrielli, P.; Pedullini, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259–9263.