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Poly Methoxy Phenols in Solution: O−H Bond Dissociation Enthalpies, Structures, and Hydrogen Bonding

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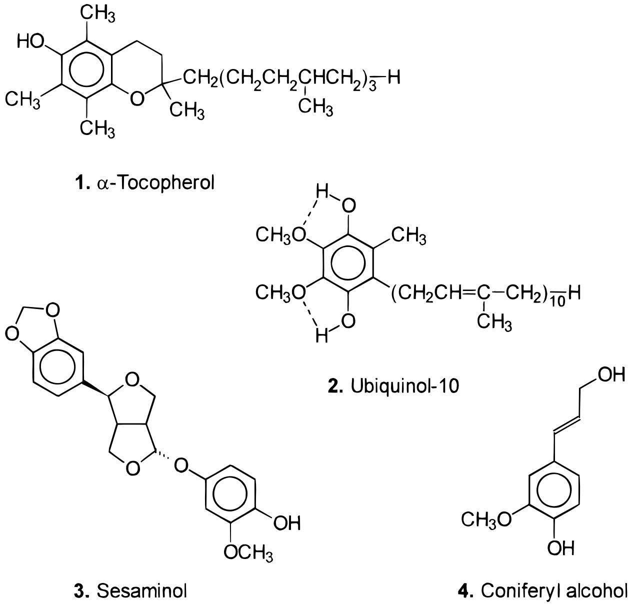
The effect of methoxy substitution on the phenolic-hydrogen bond dissociation enthalpy has been established by a photoacoustic calorimetric method and by means of density functional theory (DFT) calculations. Experimentally, the relative BDE(O−H) in kcal mol^{-1} with respect to phenol are found to be as follows: 2-methoxyphenol (−4.0), 4-methoxyphenol (−4.9), 2,6-dimethoxyphenol (−10.6), 2,4-dimethoxyphenol (−9.0), 2,4,6-trimethoxyphenol (−13.6), and ubiquinol-0 (−12.0). The intramolecular hydrogen-bond enthalpy in *o*-methoxy-substituted phenol is −4.3 kcal mol^{-1}; the intramolecularly hydrogen-bonded molecule forms an additional hydrogen bond with HBA solvents. The low BDE(O−H) for ubiquinol-0 of 78.5 kcal mol^{-1} and the protective intramolecular hydrogen bond make it a good antioxidant.

Introduction

Phenolic compounds are known to suppress the lipid peroxidation in living organisms; furthermore, they are widely used as additives in food technology. The antioxidant property can be related to the readily abstractable phenolic hydrogen as a consequence of the relatively weak bond dissociation enthalpy, BDE(O−H).[1] Besides, due to the low reactivity of the incipient aryloxyl species, radical−radical coupling prevails rather than hydrogen abstraction to sustain the oxidative chain reaction. A large variety of *o*- and/or *p*-alkoxy-substituted phenols have been identified as natural antioxidants such as α-tocopherol (**1**) and ubiquinol-10 (**2**), both present in low-density lipid proteins. Natural phenolic antioxidants can also be isolated from plants,[2] e.g., sesamolinol (**3**) from sesame seeds and coniferyl alcohol (**4**), one of the three precursors for the biosynthesis of lignin. Recently, the BDE(O−H) in α-tocopherol has been established to be 77.3 kcal mol^{-1},[3] which is 8.9 kcal mol^{-1} weaker than in unsubstituted phenol.[4] To our knowledge, the BDE(O−H) for ubiquinol-10 has not been determined.

Phenols can form intermolecular hydrogen bonds with hydrogen-bond-accepting (HBA) solvents in an equilibrium reaction to give a 1:1 complex. Since the hydrogen bond is linear, hydrogen abstraction is prevented,[5] and consequently, the apparent reactivity is reduced. Phenols with an ortho substituent with HBA properties such as methoxy are capable of creating an intramolecular hydrogen bond, which is not linear. For 2-methoxyphenol, values for the intramolecular hydrogen-bond enthalpy $\Delta H_{\text{intra-HB}}$ ranging from −2.0 to −4.1 kcal mol^{-1} have been reported.[6] For phenols with more than one methoxy substituent no information is available. Thus, in HBA solvents the two forms of hydrogen bonding may be in competition; the equilibrium ratio depends on the degree of methoxy substitution and the hydrogen bonding properties of the medium.

Scheme 1



To obtain a better understanding of the effect of methoxy substituents on the BDE(O−H) and on the inter- and intramolecular hydrogen-bonding properties, BDEs of various (poly)substituted methoxy phenols have been determined by photoacoustic calorimetry (PAC) in two

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(4) The ΔBDE value of −10 kcal mol^{-1} reported in the original article was calculated with the BDE(O−H) for phenol of 87.3 kcal mol^{-1}, which was not corrected for intermolecular hydrogen bonding with benzene (−1 kcal mol^{-1}).[3,7]

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Table 1. Experimental BDE(O−H) for Methoxy Substituted Phenols and Ubiquinol-0[a]

	benzene					ethyl acetate	
X-phenol	Δ_3H_{obs}[b]	BDE^{sol}(O−H)[c]	BDE^{gas}(O−H)[d]	BDE(O−H)[e]	ΔBDE[f]	Δ_3H_{obs}[b]	BDE^{sol}(O−H)[c]
H	−6.6	89.2	86.2	86.2	0	−2.6	93.2
2-MeO	−7.8	88.6	86.6	82.2	−4.0	−6.9	91.1
4-MeO	−18.4[g]	83.3[g]	81.3[g]	81.3[g]	−4.9	−13.5	87.8
2,6-$(MeO)_2$	−21.3	81.9	79.9	75.6	−10.6	−19.6	84.7
2,4-$(MeO)_2$	−18.0	83.5	81.5	77.2	−9.0	nd[h]	nd[h]
2,4,6-$(MeO)_3$	−27.2	78.9	76.9	72.6	−13.6	nd[h]	nd[h]
ubiquinol-0	−23.9	80.5	78.5	74.2	−12.0	n.[h]	nd[h]

[a] All values in kcal mol^{-1}, $T = 294 \pm 2$ K. [b] Average of at least three experiments. [c] Calculated by eq 4; contains contributions from inter- and intramolecular hydrogen bond enthalpies. Experimental error in BDE values is approximately ±1.5 kcal mol^{-1}. [d] Gas-phase values are obtained by removing the enthalpy of solvation of the hydrogen atom and the intermolecular hydrogen bond enthalpy: $BDE^{gas}(O-H) = BDE^{sol}(O-H) - \Delta H_{solv}(H) + \Delta H_{inter-HB}$. [e] Pure O−H BDEs, excluding all inter- and intramolecular hydrogen bond enthalpies: $BDE(O-H) = BDE^{gas} + \Delta H_{intra-HB}$. The DFT-calculated values for $\Delta H_{intra-HB}$ were used for this correction: −4.4 kcal mol^{-1} for 2-methoxyphenol and −4.3 kcal mol^{-1} for the other 2-substituted methoxy phenols (see text). [f] $\Delta BDE = BDE(O-H)_{ArOH} - BDE(O-H)_{PhOH}$. [g] Data taken from ref 3. [h] Not determined.

different solvents: benzene and ethyl acetate. Also, density functional theory (DFT) at the B3LYP/6-31G** level has been applied to calculate the bond dissociation enthalpies.

Results

Photoacoustic Calorimetry. With photoacoustic calorimetry (PAC) the reaction enthalpy is measured for the hydrogen abstraction from a phenol by a *tert*-butoxyl radical. The technique and mathematical procedures have been described in detail previously.[7,8] Di-*tert*-butyl peroxide decomposes instantaneously upon irradiation with a 337 nm laser beam (reaction 1) to give two *tert*-butoxyl radicals; subsequently, the hydrogen atom from the phenolic OH-group is abstracted (reaction 2). The apparent reaction enthalpy for the overall reaction 3, Δ_3H_{obs}, is determined by PAC.[9]

$$t\text{-BuOOBu-}t \rightarrow 2t\text{-BuO}^{\bullet} \quad (1)$$

$$t\text{-BuO}^{\bullet} + \text{ArOH} \rightarrow t\text{-BuOH} + \text{ArO}^{\bullet} \quad (2)$$

$$t\text{-BuOOBu-}t + 2\text{ArOH} \rightarrow 2t\text{-BuOH} + 2\text{ArO}^{\bullet} \quad (3)$$

The bond dissociation enthalpy of the O−H bond in solution (BDE^{sol}) can be calculated with use of eq 4, in which $(\Delta\Delta H_{solv})_{obs}$ encompasses the change in heats of solvation in the appropriate solvent for going from di-*tert*-butyl peroxide to two *tert*-butyl alcohol molecules and the volume change associated with reaction 1.[7] The constant 86.0 comprises of the heats of formation for the hydrogen atom, *tert*-butyl alcohol, and di-*tert*-butylperoxide.[10]

$$BDE^{sol}(O-H) = \frac{\Delta_3H_{obs}}{2} - \frac{(\Delta\Delta H_{solv})_{obs}}{2} + \Delta H_{solv}(H) + 86.0 \quad (4)$$

PAC measurements have been performed in several solvents: isooctane, benzene (a weak hydrogen-bond acceptor through π-electron interaction), and ethyl acetate (a strong HBA solvent). In all cases, concentrations of reagents were sufficiently high to ensure that all the heat is deposited within the photoacoustic time frame (prompt heat).[13] Values for $(\Delta\Delta H_{solv})_{obs}$ of −10 kcal mol^{-1} for isooctane, −9 kcal mol^{-1} for benzene, and −13 kcal mol^{-1} for ethyl acetate were used to derive the BDE^{sol}(O−H).[7] The enthalpy of solvation of the hydrogen atom (ΔH_{solv}(H)) is 2 ± 0.5 kcal mol^{-1} in several solvents.[15] The results are shown in Table 1. Gas-phase values can be obtained by subtracting ΔH_{solv}(H) and the intermolecular hydrogen-bond enthalpy.

To avoid intermolecular hydrogen bonding with the solvent, PAC experiments in CCl_4 would have been beneficial. In that particular solvent, a red shift occurs for all phenols investigated to result in a substantial residual absorption at 337 nm (the applied laser wavelength). The solubility of phenols in isooctane is low, and PAC measurements could be performed only with phenol and 2-methoxyphenol. As there is no interaction with the solvent in isooctane, the BDE ^{sol}(O−H) values measured in this solvent are expected to be equal to the gas-phase values, when ΔH_{solv}(H) is removed from eq 4. It was found that the Δ_3H_{obs} for phenol and 2-methoxyphenol were −9.3 and −10.1 kcal mol^{-1}, leading to BDE^{gas}(O−H) of 86.3 and 85.9 kcal mol^{-1}, respectively. In isooctane and benzene (see Table 1), the BDE(O−H) for phenol are essentially identical when the hydrogen-bond enthalpy between benzene and phenol of −1 kcal mol^{-1} is taken into account.[7]

For the *o*-methoxy-substituted phenols, the BDE^{sol}(O−H) still contains intramolecular hydrogen-bond en-

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(9) The apparent reaction enthalpy for reaction 3, Δ_3H_{obs}, is calculated from the experimentally observed fraction of the photon energy released as heat, f_{obs}

$$\Delta_3H_{obs} = \frac{84.8}{\Phi_1}(1 - f_{obs})$$

in which the constant 84.8 is the energy of the laser pulse in kcal mol^{-1} and Φ_1 is the quantum yield for reaction 1 (the photolysis of di-*tert*-butyl peroxide) in the appropriate solvent. Values for Φ_1 are 0.83 in benzene, 0.84 in isooctane, and 0.86 in ethyl acetate.[7]

(10) $\Delta_f H_{298}$ values in kcal mol^{-1}: *t*-BuOH = −74.7,[11] H• = 52.1,[11] *t*-BuOOBu-*t* = −81.6.[12]

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(13) To ensure that all heat is deposited within the photoacoustic time frame of 300 ns, the substrate concentration should be such that k_2•[ArOH] ≥ **1** × 10^7 s^{-1}.[7,8] Rate constants for hydrogen abstraction by alkoxyl radicals were measured by laser flash photolysis for all (poly)methoxy phenols except for ubiquinol-0.[14] On the basis of the rate constants for 2,4-dimethoxyphenol and 2,6-dimethoxyphenol, a low estimate is 5 × 10^8 M^{-1} s^{-1}; thus, k_2[ubiquinol-0] > 1.5 × **10**^{7} s^{-1} at the applied concentration of 0.03 M.

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(15) Enthalpies from ref 16, taking $\Delta \boldsymbol{H}_{solv}$(H) equal to $\Delta \boldsymbol{H}_{solv}$(He).

Table 2. B3LYP/6-31G//B3LYP/6-31G** BDE(O−H) for Methoxy-Substituted Phenols and Ubiquinol-0**[a]

X-phenol	BDE(O−H)[b] including $\Delta H_{\text{intra-HB}}$	BDE (O−H)[c]	ΔBDE-(DFT)[d]	ΔBDE-(PAC)[e]
H	82.8	82.8	0	0
2-MeO	80.6	76.2	−6.6	−4.0
4-MeO	77.7	77.7	−5.1	−4.9
2,6-(MeO)$_2$	77.0	72.7	−10.1	−10.6
2,4-(MeO)$_2$	75.8	71.5	−11.3	−9.0
2,4,6-(MeO)$_3$	73.4	69.1	−13.7	−13.6
ubiquinol-0	70.9[f]	66.6	−16.2	−12.0

[a] All values in kcal mol^{-1}. [b] At 298 K, contains hydrogen bond enthalpy if intramolecular hydrogen bonding is possible. [c] For the 2-substituted phenols where $\Delta H_{\text{intra-HB}}$ was not separately calculated the BDE(O−H) is corrected for intramolecular hydrogen bonding by using the obtained DFT value for 2,4-dimethoxyphenol of −4.3 kcal mol^{-1} (see text). [d] $\Delta\text{BDE} = \text{BDE(O-H)}_{\text{ArOH}} - \text{BDE(O-H)}_{\text{PhOH}}$. [e] From Table 1. [f] BDE(O−H) of the hydroxy group ortho to the methyl group; the BDE of the other O−H bond is 0.9 kcal mol^{-1} higher.

thalpies. Intermolecular hydrogen bonding with benzene can be neglected (vide infra).

In ethyl acetate as the solvent the BDE$^{\text{sol}}$(O−H) are higher (see Table 1) relative to the PAC experiments in benzene. Intermolecular hydrogen bonding with the HBA solvent now appears in the overall enthalpy balance. For example, when applying an intermolecular hydrogen-bond enthalpy for phenol and ethyl acetate of −4.7 kcal mol^{-1},[17,18] the BDE$^{\text{gas}}$(O−H) for phenol becomes 86.5 kcal mol^{-1}, within the experimental error identical to the PAC value obtained in benzene and isooctane. Thus, the difference in BDE$^{\text{sol}}$(O−H) in benzene and ethyl acetate for 4-methoxyphenol of −4.5 kcal mol^{-1} can be attributed to the $\Delta H_{\text{inter-HB}}$ in ethyl acetate, since $\Delta H_{\text{inter-HB}}$ in benzene is negligible.[3]

DFT-Computed Enthalpies. Density functional theory (DFT) calculations have been performed with use of the B3LYP functional with the 6-31G** basis set.

The computed BDE(O−H)s at 298 K are listed in Table 2. The values refer to the enthalpy differences between the lowest energy conformers of the phenolic compound (intramolecularly hydrogen bonded) and the radical. For ubiquinol-0 where two phenolic groups are present, calculations have shown that the BDE(O−H) is the lowest (difference of 0.9 kcal mol^{-1}) for the hydroxyl group ortho to the methyl substituent.

For 2-methoxyphenol and 2,4-dimethoxyphenol the conformations with the hydroxyl group oriented away from the methoxy group were calculated as well, allowing us to derive the magnitude of the intramolecular hydrogen-bond enthalpies; for 2-methoxyphenol $\Delta H_{\text{intra-HB}}$ is −4.4 kcal mol^{-1} and $\Delta G_{\text{intra-HB}}$ amounts to −4.5 kcal mol^{-1}, indicating that the change in entropy, $\Delta S_{\text{intra-HB}}$, is close to zero (0.33 eu). The $\Delta H_{\text{intra-HB}}$ found for 2,4-dimethoxyphenol is −4.3 kcal mol^{-1}, identical to $\Delta G_{\text{intra-HB}}$.

For 2,6-dimethoxyphenol and 2,4,6-trimethoxyphenol it is not possible to calculate the away conformers as local minimal energy structures. For ubiquinol-0 the steric interaction with the *o*-methyl group prevents the calculation of the $\Delta H_{\text{intra-HB}}$. For these compounds the $\Delta H_{\text{intra-HB}}$ of −4.3 kcal mol^{-1} as calculated for 2,4-dimethoxyphenol was used to compensate for the contribution of the intramolecular hydrogen bond in the computed BDE(O−H) values (see Table 2).

The ΔBDE value for 4-methoxyphenol is in accordance with an earlier reported DFT-value by Brinck et al.[19] of −5.5 kcal mol^{-1}.

DFT Conformers. In Table 3, bond lengths and spin densities are given for all calculated structures; compound numbers in the text refer to numbers in Table 3, 2nd column.

For 2-methoxyphenol two conformers were identified. The lowest energy conformation **7a** with an intramolecular hydrogen bond and the non-hydrogen-bonded form **7b** both have the hydroxy and methoxy group in the plane of the phenyl ring. The enthalpy difference between the two conformations, 4.4 kcal mol^{-1}, is the intramolecular hydrogen-bond enthalpy.[20]

For the 2-methoxyphenoxyl radical two conformers can be found, both planar, but the lowest energy conformation **7c** has the methyl group directed toward the radical oxygen and in the higher energy conformer **7d** ($\Delta H_{\mathbf{7c}\rightarrow\mathbf{7d}} = \Delta_f H(\mathbf{7d}) - \Delta_f H(\mathbf{7c}) = 1.6$ kcal mol^{-1}) the methyl group is pointing away.

For 2,6-dimethoxyphenol, the lowest energy conformation with intramolecular hydrogen bond **8a** has both methoxy groups in the phenyl plane oriented away from the hydroxy group.[21]

For the radical two conformers were found; the one with the lowest energy **8b** has both methoxy groups in the phenyl plane, one pointing toward and one away from the radical oxygen. The other conformer **8c** has both methoxy groups away from the oxygen ($\Delta H_{\mathbf{8b}\rightarrow\mathbf{8c}} = +1.0$ kcal mol^{-1}).[22]

Two conformations were found for 2,4-dimethoxyphenol. The lowest energy conformation **9a** with the intramolecular hydrogen bond has both methoxy groups in the phenyl plane, directed toward each other. The non-hydrogen-bonded form **9b** has the hydroxy group pointed away from the 2-methoxy group, which is tilted out of the phenyl plane but still oriented toward the 4-methoxy group ($\Delta H_{\mathbf{9a}\rightarrow\mathbf{9b}} = 4.3$ kcal mol^{-1}).[23]

For the radical two conformers were found, both having the two methoxy groups in the plane of the phenyl ring, the lowest energy conformer **9c** with the methyl group directed toward the radical oxygen, in the second conformer **9d** ($\Delta H_{\mathbf{9c}\rightarrow\mathbf{9d}} = 1.9$ kcal mol^{-1}) directed away.

The lowest energy conformation of 2,4,6-trimethoxyphenol **10a** is completely planar, with both *o*-methoxy groups away from the O−H, the hydrogen-bonded and the 4-methoxy group directed toward the *o*-methoxy group. In the lowest energy conformation of the radical **10b** both *o*-methoxy groups are pointing toward the

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(20) A third conformer has the methoxy group tilted out of the phenyl plane but tipped toward the hydroxy group, which is oriented away from the methoxy; the ΔH compared to **7a** is 5.3 kcal mol^{-1}.

(21) A second ground-state conformer, 0.5 kcal mol^{-1} higher in enthalpy than **8a**, has the second, not intramolecularly hydrogen bonded methoxy group twisted out of the phenyl plane. The conformation with the second methoxy group in the phenyl plane directed toward the hydroxy group appears to be a transition state ($\Delta H = 0.7$ kcal mol^{-1} compared to **8a**).

(22) Another conformation with nearly identical energies compared to **8b** ($\Delta H = 0.1$, $\Delta G = -0.1$ kcal mol^{-1}) has both methoxy groups directed toward the oxygen.

(23) A second non-hydrogen-bonded conformer was found with the 2-methoxy group tilted out of the phenyl plane but tilted toward the hydroxy group ($\Delta H = 4.6$ kcal mol^{-1} compared to **9a**).

Table 3. DFT (B3LYP/6-31G) Calculated Bond Distances and Mulliken Spin Densities**

			bond distances (Å)				Mulliken spin density[c]		
X-phenol		structure[a]	O−H	C−O(H/•)	(O)H- -O[b]	O•	C_2	C_4	C_6
H	**5a**	M	0.9663	1.3683					
	5b	R		1.2581		0.4446	0.3224	0.4054	0.3224
4-MeO	**6a**	M	0.9658	1.3721					
	6b	R		1.2559		0.4066	0.3070	0.3049	0.2379
2-MeO	**7a**	M, HB	0.9697	1.3628	2.0766				
	7b	M	0.9661	1.3665					
	7c	R, toward		1.2582		0.3975	0.1914	0.2998	0.2826
	7d	R, away		1.2496		0.3928	0.2662	0.3655	0.2693
2,6-$(MeO)_2$	**8a**	M, HB	0.9697	1.3626	2.0707				
	8b	R, toward		1.2534		0.3920	0.1920	0.2976	0.2521
	8c	R, away		1.2446		0.3762	0.2404	0.3442	0.2404
2,4-$(MeO)_2$	**9a**	M, HB	0.9691	1.3673	2.0971				
	9b	M	0.9658	1.3709					
	9c	R, toward		1.2591		0.3878	0.1560	0.2326	0.2508
	9d	R, away		1.2502		0.3792	0.2123	0.2780	0.2455
2,4,6-$(MeO)_3$	**10a**	M, HB	0.9691	1.3668	2.0901				
	10b	R, toward		1.2625		0.3931	0.1497	0.2029	0.1989
	10c	R, away		1.2467		0.3766	0.1838	0.2598	0.2354
ubiquinol-0	**11a**	M, OH 1[d]	0.9710	1.3674	2.0591				
	11a	M, OH 2[e]	0.9693	1.3739	2.2504				
	11b	R, O•1[d]		1.2583		0.3703	0.2135	0.2608	0.2050
	11b	R, OH 2[e]	0.9750	1.3484	2.0568	0.0727[f]			

[a] M = molecule, R = radical, HB = hydrogen bonded to *o*-methoxy group MeO−C_o2, away = methoxy groups oriented away from radical oxygen, toward = methoxy groups directed toward radical oxygen. [b] Length of the hydrogen bond. [c] Mulliken spin densities of other atoms not shown. [d] Positioned ortho to methyl group. [e] Positioned meta to methyl group. [f] Spin density on the oxygen of the remaining hydroxyl group.

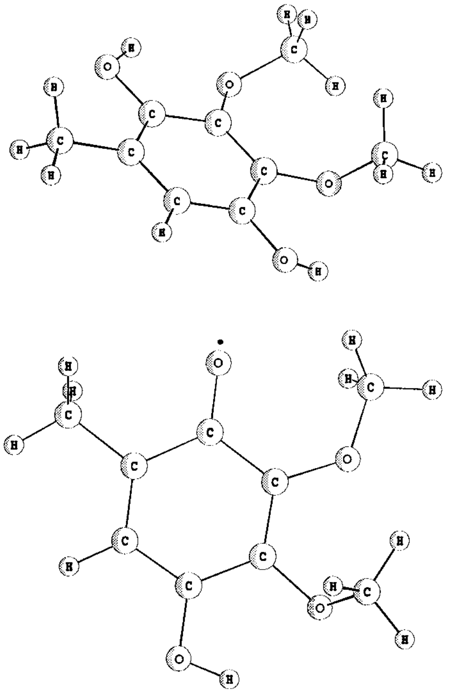

Figure 1. DFT calculated structures of ubiquinol-0 (top) and ubiquinoxyl-0 radical (bottom).

oxygen; the conformation with both methoxy groups away from the oxygen **10c** is 1.2 kcal mol^{-1} higher in enthalpy.

The DFT-calculated confomers of ubiquinol-0 and ubiquinoxyl-0 radical are shown in Figure 1. In ubiquinol-0 (**11a**), the phenolic hydrogens are hydrogen bonded to the neighboring methoxy groups. The methyl groups are tilted out of the phenyl plane by 137 and 77°, respectively. In the radical **11b** (the hydrogen from the hydroxyl group ortho to the methyl substituent is removed), the ortho methoxy group becomes planar with the methyl pointing toward the oxygen and the second hydroxyl group remains hydrogen bonded.

DFT Bond Length and Spin Densities. From Table 3, it can be inferred that the change in the phenolic O−H bond length upon intramolecular hydrogen-bond formation is quite modest: an increase of only 0.003 Å (0.3%) is found. The same holds for the C−OH bond length. In the radicals the C−O• bond length is close to that of a carbonyl bond, which was also found by Raman spectroscopy for the phenoxyl radical[24] and several para-substituted phenoxyl radicals,[25] including the 4-methoxyphenoxyl radical. The radicals in the lowest energy conformation, with the methoxy groups pointing toward the radical oxygen, have the longest C−O• bond, the difference being 0.008−0.009 Å per *o*-methoxy group oriented away from the radical oxygen. Also, the spin density on the oxygen is higher in the lowest energy conformation. This may be the result of a stabilizing interaction between the methyl of the *o*-methoxy group and the radical oxygen when the methoxy group is directed toward the oxygen.

For ubiquinol-0, the two hydrogen bonds are quite different: a strong intramolecular hydrogen bond by the hydroxy group ortho to the methyl group, bond length 2.059 Å, and one weaker hydrogen bond (2.250 Å) of the hydroxy group meta to the methyl group. When the weakest hydrogen is abstracted, the remaining hydrogen bond length is shortened to 2.057 Å, thus most likely the hydrogen-bonding enthalpy increases as well.

Discussion

Experimental Phenolic Bond Dissociation Enthalpy in $(MeO)_x$PhOH. The BDE(O−H) of phenols depends on the position and the properties of the substituents. For phenols, two separate ortho/para substituent effects have been identified. The polar effect (i.e., the

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interaction of the oxygen lone pair of the hydroxyl group with the substituent) provides an additional enthalpic contribution to the parent molecule. The radical effect gives rise to an additional enthalpic stabilization of the radical due to the interaction of the unpaired electron with the substituent. For electron-withdrawing substituents such as CN or NO_2, the stabilizing polar effect is more pronounced relative to the radical effect to result in an increase of the BDE(O−H). Conversely, electron-donating substituents such as the methoxy group have a small destabilizing polar effect and a large stabilizing radical effect, and hence, the absolute BDE(O−H) decreases.[19]

It seems reasonable to assume that the decrease by *o*- or *p*-methoxy groups of the BDE(O−H) in phenols and the BDE($O-CH_3$) in anisoles is quite similar. The same product radical is formed after O−H or $O-CH_3$ bond cleavage, and the enthalpic (polar) contribution will be weak in the closed shell molecules.[26]

A gas-phase thermolytic study with a mixture of anisole and 2-methoxyanisole has revealed that the ΔBDE($O-CH_3$) is −3.8 kcal mol^{-1}.[28] In another experimental study, the substituent effect on the BDE($O-CH_3$) has been investigated by applying a low-pressure pyrolysis method;[29] the ΔBDE($O-CH_3$) for the 4-MeO group was found to be −4.2 kcal mol^{-1}, which is close to our PAC value of −4.9 kcal mol^{-1} for 4-methoxyphenol.

When the increment for 2-methoxyanisole is applied to the PAC value for 2-methoxyphenol, the BDE(O−H) in 2-methoxyphenol is expected to be 82.4 kcal mol^{-1} (see Table 1). The difference of −4.2 kcal mol^{-1} with the experiment (in benzene) can be identified as the enthalpic contribution due to the intramolecular hydrogen bond and is in perfect agreement with the DFT-calculated value of −4.4 kcal mol^{-1}.[30]

Experimental studies, comprising photoacoustic calorimetry and electrochemical methods, have revealed that a clear linear correlation exists between the relative BDE(O−H) for para-substituted phenols and the Brown substituent constant σ^+;[3,32,33] the ortho-substituted phenols could be fitted by adopting $\sigma_o^+ = 0.66\sigma_p^+$.[3,33]

To assess the validity of the correlation with σ^+ for $(MeO)_xPhOH$, the contribution of the intramolecular hydrogen bond enthalpies needs to be removed. Thus, a constant value of −4.3 kcal mol^{-1} (as has been found by DFT calculations and by analogy with the anisoles, vide supra) has been subtracted from the experimental BDE(O−H)^{sol} as measured in benzene for the all the *o*-methoxy-substituted phenols. As the methoxy substituent predominately influences the stability of the product radicals,[34] it is not likely that the strength of the intramolecular hydrogen bond in the parent phenols varies significantly. The ΔBDE(O−H) obtained in this way are given in Table 1, column 6. A plot of the ΔBDE(O−H) versus $\Sigma\sigma^+$, with use of σ_p^{+}[35] and σ_m^{+},[36] yields a straight line (see Figure 2) with eq 5 as the linear regression. The ΔBDE(O−H) for α-tocopherol (−8.9 kcal mol^{-1})[3,4] is also presented in Figure 2.

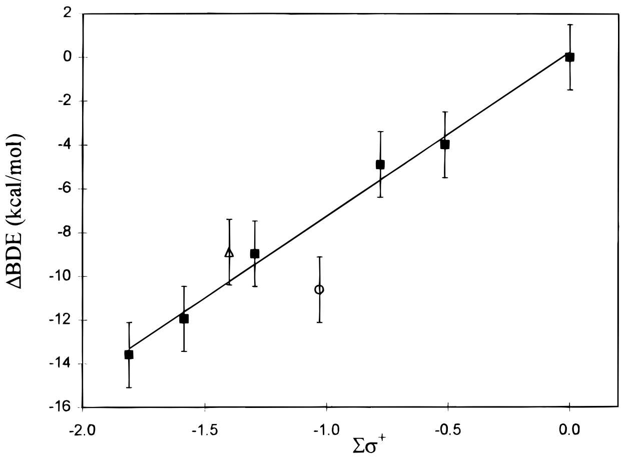

Figure 2. Plot of ΔBDE(O−H) [BDE(ArOH) − BDE(PhOH)] with error limits of ±1.5 kcal mol^{-1}, vs $\Sigma\sigma^+$. The squares were used to obtain eq 5 and represent from left to right phenol, 2-methoxyphenol, 4-methoxyphenol (taken from ref 3), 2,4-dimethoxyphenol, ubiquinol-0, and 2,4,6-trimethoxyphenol. The circle represents 2,6-dimethoxyphenol and the triangle α-tocopherol (taken from ref 3); both are not used in the correlation.

$$\Delta \mathrm{BDE(O-H)} = 7.49\Sigma\sigma^+ - 0.23\ (r^2 = 0.992) \quad (5)$$

This correlation is, given the experimental uncertainties, quite similar to those found by Jonsson et al.[33] (ΔBDE = $7.14\Sigma\sigma^+ - 0.47$) and by Wayner et al.[3] (ΔBDE = $7.32\Sigma\sigma^+ - 0.64$). Hence, the BDE(O−H) in any polysubstituted phenolic compound can be estimated with a high degree of precision, provided that the contribution by intramolecular hydrogen bonding is properly accounted for.

Our absolute BDE^{gas}(O−H) values in benzene deviate from those reported by Lucarini et al.,[37] as determined by an EPR equilibration method, by 2−3 kcal mol^{-1}, but the relative BDE(O−H) for 2,4,6-trimethoxyphenol com-

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[26] A computational study[27] has shown that ΔBDE(O−H) and ΔBDE($O-CH_3$) are almost identical for electron-donating substituents. For example, for 4-methoxyphenol and 4-methoxyanisole the computed ΔBDE values are −7.08 kcal mol^{-1} and −7.0 kcal mol^{-1}, respectively. These values deviate from the experimental ΔBDEs known for these compounds, but illustrate clearly that substituent effects are similar for anisoles and phenols.

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(28) Schraa, G.-J.; Arends, I. W. C. E.; Mulder, P. *J. Chem. Soc., Perkin Trans. 2* **1994**, 189−97.

(29) Suryan, M. M.; Kafafi, S. A.; Stein, S. E. *J. Am. Chem. Soc.* **1989**, *111*, 1423−9.

(30) Another DFT value reported by Wright et al.[31] for the intramolecular hydrogen bond enthalpy in 2-methoxyphenol is −5.7 kcal mol^{-1}, high compared to our results and also higher than can reasonably be expected for this bond. Possibly the conformation for the non-hydrogen-bonded molecule used in these calculations was not the lowest energy conformer, but the conformation with the methyl of the methoxy group directed toward the hydroxy group (see also ref 20).

(31) Wright, J. S.; Carpenter, D. J.; McKay, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 4245−52.

(32) (a) Mulder, P.; Saastad, O. W.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 4090−2. (b) Bordwell, F. G.; Zhang, X.-M.; Satish, A. V.; Cheng, J.-P. *J. Am. Chem. Soc.* **1994**, *116*, 6605−10.

(33) Jonsson, M.; Lind, J.; Erikson, T. E.; Merényi, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1567−8.

(34) This is confirmed by our DFT results: the enthalpies for the two isodesmic reactions, PhOH + 2,6-$(MeO)_2PhOH \rightarrow$ 2 2-MeOPhOH, 4-MeOPhOH + 2,4,6-$(MeO)_3PhOH \rightarrow$ 2 2,4-$(MeO)_2PhOH$, are 4.7 and 4.0 kcal mol^{-1}, respectively, which is attributed to the formation of a second intramolecular hydrogen bond. This means that substitution with methoxy groups is purely additive and confirms that the polar effect in the closed shell molecules is small.

(35) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−95.

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(37) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259−63.

pared to 2,6-dimethoxyphenol is in good agreement with our study.[38]

The DFT Phenolic Bond Dissociation Enthalpy in (MeO)$_x$PhOH. DFT calculations generally do not provide very accurate absolute BDEs for bonds involving the element oxygen,[39] as can be seen from the results for phenol: DFT underestimates the BDE(O−H) by 3.4 kcal mol^{-1} (calculated 82.8 kcal mol^{-1}; experimental 86.2 kcal mol^{-1}). When, however, the relative BDE(O−H) values are compared, see Table 2, a fair agreement is obtained with ubiquinol-0 as the clear exception. Moreover, the calculated absolute hydrogen bond enthalpies are in perfect agreement with experimental results.

Conformations of *o*-Methoxyphenols in Solution. According to our DFT results, the entropy change for intramolecular hydrogen bond formation $\Delta S_{\text{intra-HB}}$ is close to zero, as was already suggested some 40 years ago by Jaffé.[40] A rationale is that the contribution of the free O−H vibration to the overall entropy is already negligible. Thus, with the $\Delta G_{\text{intra-HB}}$ of −4.5 kcal mol^{-1}, the equilibrium constant, $K_{\text{intra-HB}}$, becomes 2.0 × 10^3 for 2-methoxyphenol. Hence, in non-HBA solvents less than 0.1% exist as the free phenol. This is in agreement with the findings of Spencer et al.,[6a,41] who used IR spectroscopy and found that HBA solvents such as diethyl ether, THF, and di-*n*-butyl sulfide did not disrupt the intramolecular hydrogen bond in 2-methoxyphenol.[42] Only with DMSO, a very potent HBA solvent, could an equilibrium constant for the intermolecular hydrogen bond formation be determined as $K_{\text{inter-HB}} = 3.75$ M^{-1} at 298 K.

The equilibrium constant for intermolecular hydrogen bonding of phenol with ethyl acetate, $K_{\text{inter--HB}}$, ranges from 9.0 ± 0.4[18] to 6.6 M^{-1} [43] (average 7.8 M^{-1}).[44] Hence, in pure ethyl acetate (10 M) and at 298 K the free phenol concentration is around 1%.[45]

In non-HBA solvents 2-methoxyphenol (and other *o*-methoxy-substituted phenols) exists as the intramolecularly hydrogen-bonded conformer. However, our PAC results show that the apparent BDE(O−H) in ethyl acetate is higher (2.5 kcal mol^{-1}) than in benzene (see Table 1), which is caused by an additional interaction of the phenolic compound with the solvent. In principle, 2-methoxyphenol in solution may be present as four different entities **A**−**D** (see Figure 3). Supposing that $K_{\text{inter-HB}}$ is similar to that for phenol, the ratio between **A** and **C** becomes (7.8 × 10)/2 × 10^3, implying that ca. 4% is converted into **A**, and while 96% remains **C**, the concentration of **B** is negligible. This minor change in the concentration of **C** cannot explain the observation made by PAC. Therefore, a solvent interaction with **C** is more likely.

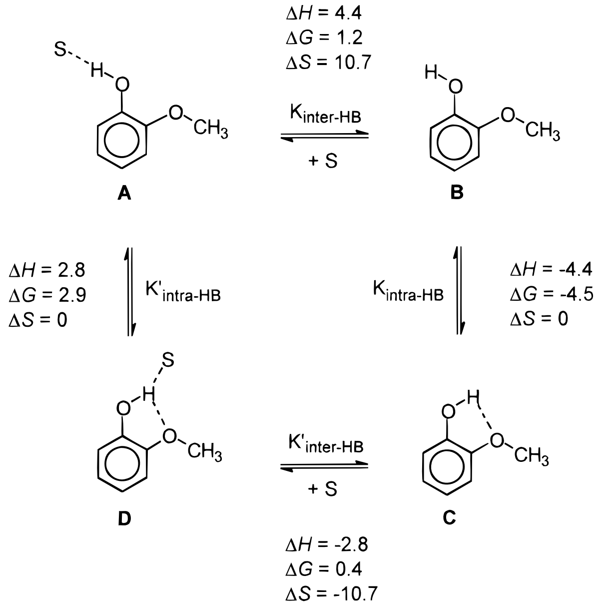

Figure 3. Four possible forms of 2-methoxyphenol in a HBA solvent. Energetics for hydrogen bonding of 2-methoxyphenol in ethyl acetate for the reactions in clockwise direction (see text), ΔH and ΔG in kcal mol^{-1}, ΔS in cal mol^{-1} K^{-1}.

From kinetic measurements, the equilibrium constant $K'_{\text{inter-HB}}$ for hydrogen-bond formation between the intramolecularly hydrogen-bonded complex and ethyl acetate for 2-methoxyphenol (and 2,6-dimethoxyphenol) has been found to be 0.5 M^{-1},[14] meaning that the ratio of **A**/**B**/**C**/**D** = 0.6:0:14:85. Adopting $\Delta S'_{\text{inter-HB}}$ of −10.7 cal mol^{-1} K^{-1},[47] the strength of the intermolecular hydrogen bond for **C** with ethyl acetate becomes −2.8 kcal mol^{-1}. Thus, for 2-methoxyphenol relative to the open non-hydrogen-bonded structure (**B**), **D** is stabilized by −2.8 + −4.4 = −7.2 kcal mol^{-1}. Removal of the phenolic hydrogen by *tert*-butoxyl radicals (reaction 2) can only occur from **C**, and in order to restore the equilibrium condition between **C** and **D**, an additional enthalpy of 0.85 × −2.8 = −2.4 kcal mol^{-1} is required. This is within experimental error in agreement with our PAC results for 2-methoxyphenol (−2.5) and for 2,6-dimethoxyphenol (−2.8 kcal mol^{-1}). It should be noted that for phenols with two *o*-methoxy groups only structure types **C** and **D** can exist.

Ubiquinol as Antioxidant. The BDE(O−H) found for ubiquinol-0 of 78.5 ± 1.5 kcal mol^{-1}, including the intramolecular hydrogen bond, indicates that the antioxidant property is comparable with α-tocopherol (BDE-

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[38] Reported BDE(O−H) values: phenol 88.3 kcal mol^{-1}, 4-methoxyphenol 82.8 kcal mol^{-1}, 2,6-dimethoxyphenol 83.2 kcal mol^{-1}, 2,4,6-trimethoxyphenol 80.0 kcal mol^{-1}.[37]

[39] van Scheppingen, W. B.; Dorrestijn, E.; Arends, I. W. C. E.; Mulder, P.; Korth, H.-G. *J. Phys. Chem. A* **1997**, *101*, 5404−11.

[40] Jaffé, H. H. *J. Am. Chem. Soc.* **1957**, *79*, 2373−5.

[41] Spencer, J. N.; Heckman, R. A.; Harner, R. S.; Shoop, S. L.; Robertson, K. S. *J. Phys. Chem.* **1973**, *77*, 3103−6.

[42] Theoretically, the equilibrium between structure C and D should be visible with IR spectroscopy. In the IR experiments performed by Spencer et al.,[6a,41] low concentrations were used in carbon tetrachloride: 2-methoxyphenol 0.002−0.004 M, diethyl ether, THF, and di-*n*-butyl sulfide 0.1−0.2 M, DMSO 0.003 M. Because of the low $K_{\text{inter-HB}}$ values for the formation of the additional hydrogen bond between intramolecularly hydrogen bonded 2-methoxyphenol and the solvent molecules, the change in concentration of C could probably not be detected by the IR method and concentrations used, except with the strongest hydrogen-bond acceptor DMSO.

[43] Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1996**, *118*, 6790−1.

[44] $K_{\text{inter-HB}}$ is an apparent value, since the chemical potential (activity coefficient) changes when the concentration of solute increases (i.e., going to pure ethyl acetate).

[45] Recently, the intermolecular hydrogen-bond enthalpy between phenol and water in the gas-phase has been determined to be −5.60 ± 0.11 kcal mol^{-1}.[46] When using $\Delta S_{\text{inter-HB}}$ of −10.7 cal mol^{-1} K^{-1},[47] $K_{\text{inter-HB}}$ becomes 59 M^{-1}, and consequently, the free phenol concentration in water will be as low as 0.03%.

[46] Courty, A.; Mons, M.; Dimicoli, I.; Piuzzi, F.; Brenner, V.; Millié, P. *J. Phys. Chem. A* **1998**, *102*, 4890−8.

[47] Adopting the average equilibrium constant of 7.8 M^{-1} for the intermolecular hydrogen bond formation between B and ethyl acetate, and −4.4 kcal mol^{-1} for $\Delta H_{\text{inter-HB}}$ (the average of −4.7 kcal mol^{-1} for phenol and ethyl acetate[17,18] and −4.1 kcal mol^{-1} for 4-methoxyphenol and acetonitrile,[48] which possesses similar HBA properties), $\Delta G_{\text{inter-HB}}$ becomes −1.2 kcal mol^{-1}, and $\Delta S_{\text{inter-HB}}$ becomes −10.7 cal mol^{-1} K^{-1}. For the formation of the additional intermolecular hydrogen bond of C and ethyl acetate the entropy change is expected to be the same.

(O−H) of 77.3 kcal mol^{-1})^3. It has been found by Foti et al.[49] that hydrogen abstraction from ubiquinol by phenoxyl radical was independent of the length of the hydrophobic tail; essentially the same rate constants were found for ubiquinols with different tail lengths, from 0 (ubiquinol-0) to 10 (ubiquinol-10) isoprenoid units. According to the relationship between degree of substitution and the BDE(O−H) (vide supra), it can be expected that also BDE(O−H) will be the same for all ubiquinols, since the influence of a meta alkyl group on the BDE(O−H) (σ_m+ for alkyl is around −0.07 [36]) is less than 1 kcal mol^{-1}.

In ubiquinol-0, the two methyl groups of the methoxy substituents are forced out of the phenyl plane (see Figure 1), but in the ubiquinoxyl radical the *o*-methoxy group is again in the plane of the phenyl ring, maximizing the conjugation with the radical center. As the ΔBDE(O−H) of ubiquinol-0 nicely fits our correlation (see Figure 2), this confirms that the loss of conjugation in the parent molecule by the nonplanarity of the methoxy groups has little if any impact on the strength of the phenolic hydrogen bond.

In ubiquinol the intramolecular hydrogen bond protects the hydroxyl group against strong intermolecular interactions; hence, an appreciable amount of hydrogens remain available for antioxidant activity, even in polar solvents. Therefore, on the basis of kinetic and thermodynamic data now available, ubiquinol is likely to be a better antioxidant than α-tocopherol, which is not protected against intermolecular hydrogen bonding.

Experimental Section

Photoacoustic Calorimetry. The PAC setup and experimental procedure have been described before;[7,8] 2-hydroxybenzophenone was used as a calibrating compound. Concentration of phenols used in benzene: phenol 0.1 M, 2-methoxyphenol 0.25−0.5 M, 4-methoxyphenol 0.1−0.2 M, 2,6-dimethoxyphenol 0.1−0.2 M, 2,4-dimethoxyphenol 0.1−0.2 M, 2,4,6-trimethoxyphenol 0.03−0.1 M, ubiquinol-0 0.03−0.04 M. In ethyl acetate: phenol 1.0 M, 2-methoxyphenol 1.0 M, 4-methoxyphenol 0.25−0.5 M, 2,6-dimethoxyphenol 0.25 M. In isooctane: phenol 0.1 M, 2-methoxyphenol 0.25−0.5 M.

Chemicals. Isooctane, ethyl acetate (spectroscopic quality), and benzene (HPLC grade) were distilled before use. 2-Hydroxybenzophenone was recrystallized three times from ethanol. Di-*tert*-butyl peroxide was passed over alumina directly before use. Phenol (Merck) was recrystallized twice from hexane or petroleum ether 40−60, 2-methoxyphenol (Aldrich) was vacuum distilled, and 4-methoxy- and 2,6-dimethoxyphenol were sublimed. 2,4-Dimethoxyphenol and 2,4,6-trimethoxyphenol were synthesized according to a literature procedure[50] from the corresponding benzaldehydes and further purified by vacuum distillation. After crystallization, 2,4,6-trimethoxyphenol was recrystallized from petroleum ether 40−60 with ±10% benzene. Ubiquinol-0 was obtained by reduction of ubiquinone-0 with $Na_2S_2O_4$.

Density Functional Theory Calculations. The calculations were performed with Gaussian 94 rev. E.3 package on an IBM RS6000 computer and a Silicon Graphics Indy workstation. The B3LYP method with the 6-31G** basis set was employed for geometry optimization and the frequency routines. The basis set was chosen to obtain optimum results with respect to accuracy and calculation time. The zero point vibrational energy (ZPVE) corrections were scaled by a factor 0.9806 to account for anharmonicity.[51]

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(50) Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* **1984**, *49*, 4740−1.

(51) Scott, P. A.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−13.