J. Am. Chem. Soc. **2000,** *122,* 2355−2360

Hydrogen Atom Abstraction Kinetics from Intramolecularly Hydrogen Bonded Ubiquinol-0 and Other (Poly)methoxy Phenols

Martine I. de Heer,[†] **Peter Mulder,***[,†] **Hans-Gert Korth,**[‡] **Keith U. Ingold,***[,§] **and Janusz Lusztyk**[§]

Contribution from the Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300RA Leiden, The Netherlands, Institut für Organische Chemie, Universität-GH Essen, D-45117 Essen, Germany, and Steacie Institute for Molecular Sciences, National Research Council of Canada, Ottawa, Ontario, Canada K1A OR6

Received October 20, 1999. Revised Manuscript Received December 16, 1999

Abstract: The effect of methoxy substitution on the abstraction of the phenolic hydrogen atom involved in intramolecular hydrogen bonding by *tert*-butoxyl and cumyloxyl radicals has been investigated by laser flash photolysis. Also transition state calculations for methoxyl radical and 2-methoxyphenol have been carried out by a density functional theory (DFT) method. Hydrogen atom abstraction is surprisingly easy from intramolecularly hydrogen bonded methoxyphenols, in contrast to intermolecularly hydrogen bonded molecules. The kinetic solvent effect, investigated in six solvents with different hydrogen bond accepting properties, on the hydrogen atom abstraction reaction from *o*-methoxy phenols was shown to be smaller than for non-hydrogen bonded phenols, and is independent of further methoxy substitution. The high rate constant for hydrogen atom abstraction from ubiquinol-0 (2.8×10^9 M^{-1} s^{-1} in CCl_4) and the small kinetic solvent effect make it a good antioxidant, even in a polar environment.

Introduction

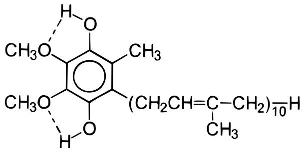
Many natural antioxidants are alkoxy-substituted phenolic compounds, which can trap peroxyl radicals by donating a hydrogen atom. Two phenolic antioxidants, α-tocopherol and ubiquinol-10, are important in the protection of human low-density lipoproteins (LDL). In homogeneous solution peroxyl radicals abstract the phenolic hydrogen from α-tocopherol, ArOH, and the resulting α-tocopheroxyl radical, $ArO^\bullet$, then scavenges a second peroxyl radical forming nonradical products.[1] However, in LDL an alternative pathway is possible for the α-tocopheroxyl radical: it can abstract a hydrogen atom from a lipid molecule, thus creating an oxidative chain reaction known as tocopherol-mediated peroxidation, TMP.[1] This TMP process is inhibited by ascorbate in the aqueous phase and by ubiquinol-10, $Q_{10}H_2$, in the lipid of the LDL particle. The $Q_{10}H_2$ is believed to inhibit TMP by donating a phenolic hydrogen atom to the α-tocopheroxyl radical, reaction 1. The resultant semiquinone radical or radical anion reacts with dioxygen to yield the quinone and the water-soluble superoxide radical

$$ArO^\bullet + Q_{10}H_2 \rightarrow ArOH + Q_{10}H^\bullet \qquad (1)$$

$$Q_{10}H^\bullet\,(Q_{10}{}^{\bullet-}) + O_2 \rightarrow Q_{10} + O_2{}^{\bullet-} + (H^+) \qquad (2)$$

anion which escapes from the LDL particle and thus stops the TMP. In $Q_{10}H_2$ the phenolic hydrogens are intramolecularly bonded. Thus, reaction 1 involves the abstraction of an intramolecularly hydrogen-bonded phenolic hydrogen atom.

More interestingly, it has been firmly established that phenolic hydrogen atoms involved in intermolecular hydrogen bonds are not abstracted.[2−4] This raises the pertinent question: Are intramolecularly hydrogen-bonded phenols really reactive toward free radicals? Herein, we show using *o*-methoxyphenols that their phenolic hydrogen atoms are abstracted by radicals surprisingly readily.


$Q_{10}H_2$
Ubiquinol-10

The antioxidant activity of substituted phenols can be related to the bond dissociation enthalpies of the phenolic O−H bonds, BDE(O−H). In previous studies,[5,6] BDE(O−H)s have been determined by using a photoacoustic calorimetry technique for α-tocopherol[6] and several *o*-methoxy-substituted phenols, including ubiquinol-0, Q_0H_2, the simplest ubiquinol, which lacks the 10 isoprenoid units of $Q_{10}H_2$.[5] From these studies it can be inferred that reaction 1 is slightly endothermic. It was found that 2-methoxyphenol was almost entirely intramolecularly hydrogen bonded even in strong hydrogen bond accepting (HBA) solvents.[5] Nevertheless, a thermodynamic solvent effect was observed, suggesting an additional interaction between the

---

[†] Leiden University.

[‡] Universität-GH Essen.

[§] National Research Council of Canada.

(1) Bowry, V. W.; Ingold, K. U. *Acc. Chem. Res.* **1999**, *32*, 27−34.

(2) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929−30.

(3) MacFaul, P. A.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 1316−21.

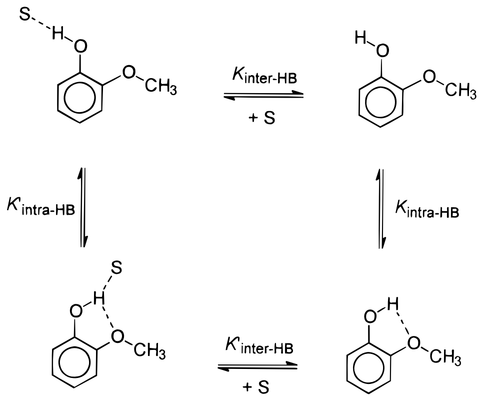
(4) Valgimigli, L.; Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1995**, *117*, 9966−71.

(5) de Heer, M. I.; Korth, H. G.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 6969−75.

(6) Wayner, D. D. M.; Lusztyk, E.; Ingold, K. U.; Mulder, P. *J. Org. Chem.* **1996**, *61*, 6430−3.

10.1021/ja9937674 CCC: $19.00

Scheme 1



intramolecularly bonded hydrogen and a solvent molecule. Thus, 2-methoxyphenol in a HBA solvent can be present in four different forms, see Scheme 1.

Intermolecular hydrogen bonding with the solvent prevents hydrogen atom abstraction, as has been observed for many different HBA solvents, and the magnitude of the kinetic solvent effect is independent of the nature of the abstracting radical.[2,4] To determine whether hydrogen atom abstraction is possible from the intramolecularly hydrogen-bonded phenols, rate constants have been measured by laser flash photolysis (LFP) for the hydrogen atom abstraction by alkoxyl (*tert*-butoxyl and cumyloxyl) radicals from various (poly)methoxy phenols including Q_0H_2 in solvents with different HBA properties. In addition, transition state structures for hydrogen atom abstraction from free and intramolecularly hydrogen-bonded 2-methoxyphenol by the methoxyl radical were calculated by a density functional theory (DFT) method.

Results

Laser Flash Photolysis. The rate constants for hydrogen atom abstraction from methoxyphenols by alkoxyl radicals were measured by laser flash photolysis (LFP). *tert*-Butoxyl or cumyloxyl radicals were generated from the corresponding dialkyl peroxides.[7] Upon irradiation of a solution of the peroxide and the phenol under investigation, the peroxide decomposes “instantaneously” to give two alkoxyl radicals, reaction 3, which then abstract the hydroxylic hydrogen atom, reaction 4. The rate constants were measured by monitoring the pseudo-first-order growth of the phenoxyl radical for 4-methoxyphenol, 2,4-dimethoxyphenol, and ubiquinol-0. In the case of 2-methoxyphenol and 2,6-dimethoxyphenol, the growth of the phenoxyl radicals could not be monitored directly because of their low extinction coefficients. Instead, the pseudo-first-order decay of the cumyloxyl radical was measured.

$$\mathrm{ROOR} \rightarrow 2\mathrm{RO}^{\bullet} \qquad (3)$$

$$\mathrm{RO}^{\bullet} + \mathrm{ArOH} \rightarrow \mathrm{ROH} + \mathrm{ArO}^{\bullet} \qquad (4)$$

The effects of six solvents with different HBA properties on the kinetics of reaction 4 are summarized in Table 1.

For 4-methoxyphenol, the only phenol examined with no possibility of forming an intramolecular hydrogen bond, a large solvent effect is observed. The rate constant decreases by a factor of ca. 30 on changing from the poor hydrogen bond-accepting solvent, tetrachloromethane, to the strong hydrogen bond-accepting solvent, ethyl acetate. The rate constant in tetrachloromethane is high and close to the diffusion-controlled limit. For the *o*-methoxyphenols on changing the solvent from CCl_4 to ethyl acetate the decrease in rate constants is smaller, with an average of ca. 6 for 2-methoxy-, 2,4-dimethoxy-, and 2,6-dimethoxyphenol and ubiquinol-0. Thus, the presence of an intramolecular hydrogen bond attenuates the kinetic solvent effect arising from intermolecular hydrogen bonding but does not completely eliminate it.[11,13]

The two hydroxyl groups of ubiquinol-0 are not equivalent, the hydroxyl group ortho to the methyl group (OH_a) has been calculated by DFT to have a somewhat lower BDE(O−H) and to form a slightly stronger intramolecular hydrogen bond than the hydroxyl group meta to the methyl group (OH_b).[5,15] The difference in BDE(O−H) is however quite small (0.9 kcal mol^{-1} by DFT calculations), so hydrogen atom abstraction from both hydroxyl groups will be feasible.

DFT-Calculated Transition States for Hydrogen Atom Abstraction. Density functional theory calculations on the B3LYP/6-31G(d,p) level have been performed for the transition states for hydrogen atom abstraction by the methoxyl radical (as a computational model for *tert*-butoxyl and cumyloxyl) from hydrogen-bonded and non-hydrogen-bonded 2-methoxyphenol and the structures are given in Figure 1. The O−H−O angle in both transition state structures is similar, 162.9° in the hydrogen-bonded form and 162.4° in the non-hydrogen-bonded form.

In the ground state structures only a small increase of the O−H bond length is observed in the hydrogen-bonded form compared to the non-hydrogen-bonded form of 2-methoxyphenol, see Figure 2. In the transition state, however, the O−H bond is more elongated and the OH−methoxyl radical distance is significantly shorter in the hydrogen-bonded form, indicating a “later” transition state. Intramolecular hydrogen bonding in the transition state also keeps the phenolic OH group much closer to the plane of the aromatic ring (dihedral angle 14.6°) than is the case for the non-hydrogen-bonded form where the OH group is twisted out of the aromatic ring plane by about 25° in the transition state. The hydrogen atom abstraction from the hydrogen-bonded form occurs as a synchronous lengthening

---

[7] The reactivity of both alkoxyl radicals for hydrogen atom abstraction is essentially the same.[4]

[8] Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 521−29.

[9] Calculated from the equilibrium constants (Table 3) and the concentration of the pure solvent. The equilibrium constants in Table 3 are calculated with eq 5 and the solvent concentration as used in the experiment: 100 vol % for 2-methoxy- and 2,6-dimethoxyphenol and 70 vol % in the case of 4-methoxyphenol, 2,4-dimethoxyphenol, and ubiquinol-0; β_2^{H} for di-*tert*-butyl peroxide is set at zero. If appropriate the k_4 is recalculated by using the equilibrium constants, the concentration of the pure solvent, and eq 5.

[10] Snelgrove, D. W.; Banks, J. T.; Lusztyk, J.; Mulder, P.; Ingold, K. U. Manuscript in preparation.

[11] Rate constants for hydrogen atom abstraction by *tert*-butoxyl radicals from 4-methoxyphenol and 2-methoxyphenol of 1.6×10^9 and 1.7×10^8 M^{-1} s^{-1}, respectively, in 1:2 benzene−di-*tert*-butyl peroxide, have been reported.[12]

[12] Das, P. K.; Encinas, M. V.; Steenken, S.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 4162−6.

[13] Relative rate constants reported by Bors et al.[14] for hydrogen atom abstraction by alkoxyl radicals from 2-MeO-, 4-MeO-, and 2,6-$(MeO)_2$-PhOH in aqueous solution (1:2.5:7.5) and for 2-MeO- and (2,6-$MeO)_2$-PhOH (1:1.3) in *n*-hexane deviate from the relative rate constants for these compounds calculated from the absolute rate constants measured in our study; with CCl_4 as the solvent the ratio for 2-MeO-, 4-MeO-, and 2,6-$(MeO)_2$-PhOH equals 1:31:2.6.

[14] Bors, W.; Michel, C.; Saran, M. *Biochim. Biophys. Acta* **1984**, *796*, 312−9.

[15] The conformation of the two methoxy groups in Q_0H_2 is different, the one ortho to OH_b is twisted further out of the phenyl plane, which gives rise to a longer hydrogen bond length and thus a weaker hydrogen bond. The higher overall BDE(O−H) of OH_b is caused by the effect of the position of methyl substituent.

Table 1. Rate Constants, k_4, for Hydrogen Atom Abstraction from (Poly)methoxy Phenols by Alkoxyl Radicals

		k_4 (10^{-7} M^{-1} s^{-1}) for (poly)methoxy phenols[a]				
solvent	β_2^{H} [b]	2-MeO[c]	2,6-(MeO)$_2$[c]	2,4-(MeO)$_2$[d]	ubiquinol-0[d]	4-MeO[d,e]
pentane	0.00	11				
tetrachloromethane	0.05[f]	9.3	24	86	280	300
benzene	0.14	8.2	18	76 (72)	220 (200)	230 (210)
anisole	0.26	3.7	10			
acetonitrile	0.44	1.6	4.4	21 (16)	43 (31)	13 (9.1)
ethyl acetate	0.45	1.5	4.2	22 (17)	56 (42)	14 (10)
tert-butyl alcohol	0.49	1.3	6.7	15 (10)	49 (36)	5.9 (4.0)

[a] Error in k_4 approximately ±10%. [b] Values from ref 8. [c] LFP at 308 nm, with 0.13 M dicumyl peroxide. [d] LFP at 337 nm, with 30 vol % di-*tert*-butyl peroxide. Values in parentheses are recalculated for the pure solvent.[9] β_2^{H} for di-*tert*-butyl peroxide is set at 0. [e] Similar values are obtained from competitive kinetic studies, ref 10. [f] For tetrachloromethane a β_2^{H} of 0.05 is used, instead of 0.0 from ref 8, see ref 10.

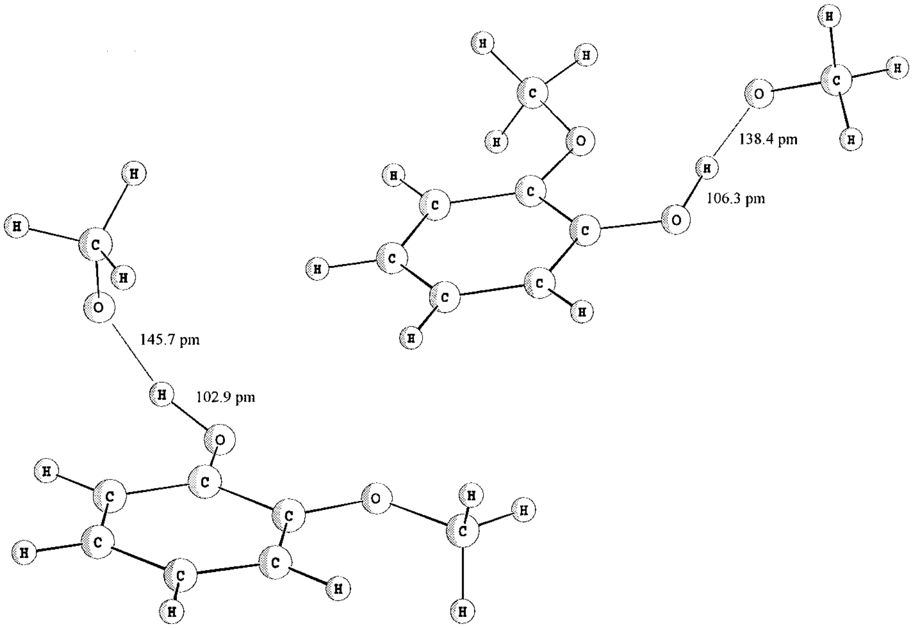


Figure 1. B3LYP/6-31G(d,p)-calculated transition state structures for hydrogen abstraction by methoxyl radical from intramolecularly hydrogen-bonded (top right) and non-hydrogen-bonded 2-methoxyphenol. The C_2-C_1-O-H torsion angle is 14.6° in the hydrogen-bonded transition state and 25.1° in the non-hydrogen-bonded situation.

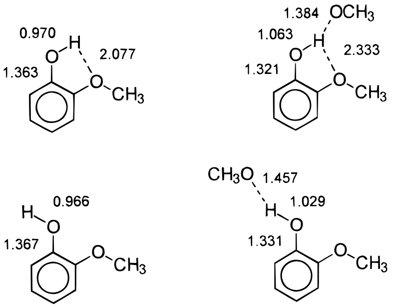


Figure 2. Ground state and transition state structures for the hydrogen abstraction by methoxyl radical from hydrogen-bonded and non-hydrogen-bonded 2-methoxyphenol, with relevant bond lengths in angstroms.

Table 2. B3LYP/6-31G(d,p)//B3LYP/6-31G(d,p)-Calculated Thermochemical Data for Hydrogen Abstraction from 2-Methoxyphenol by Methoxyl Radical[a]

	transition state		hydrogen abstraction	
ground state	$\Delta H^{\ddagger}_{298}$	$\Delta G^{\ddagger}_{298}$	$\Delta_4 H_{298}$	$\Delta_4 G_{298}$
hydrogen bonded	−5.1	+4.3	−16.1	−16.2
non-hydrogen bonded	−7.6	+2.5	−20.5	−20.7

[a] All values in kcal mol^{-1}.

of the O−H bond and the intramolecular hydrogen bond, and a shortening of the newly formed MeO−H bond.

Unfortunately, numerous attempts to calculate the analogous transition state structure for hydrogen atom abstraction from 4-methoxyphenol by methoxyl radical were unsuccessful. Either transition structures were obtained which, according to vibrational analysis, corresponded to rotational barriers in 4-methoxyphenol-methoxyl complexes, or the optimization cycles displayed an irregular “oscillatory” behavior between states of about 0.4 kcal mol^{-1} difference in electronic energy (though the relevant geometrical parameters were close to those expected for the transition structure). The O−H−O angle was always around 170°.[16]

The relative Gibbs free energy change, $\Delta\Delta G^{\ddagger}_{298}$, for the hydrogen atom abstraction from the non-hydrogen-bonded 2-methoxyphenol is favored by 1.8 kcal mol^{-1} (Table 2), which would cause the rate of hydrogen atom abstraction from the non-hydrogen-bonded form to be 20 times as great as that from the hydrogen-bonded form.[18] For both transition states, a negative activation enthalpy and a large negative activation entropy are predicted. The differences in reaction enthalpy

---

(16) Tanaka et al.[17] computed transition states for hydrogen atom abstraction from several para-substituted phenols by hydroperoxyl and methylperoxyl radicals at the HF/STO-3G level, finding O−H−O angles of 180°, in contrast to our results for *o*- and *p*-methoxyphenol.

(17) Tanaka, K.; Sakai, S.; Tomiyama, S.; Nishiyama, T.; Yamada, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2677−80.

Δ_4H_{298} and reaction free energy change Δ_4G_{298}, −4.4 and −4.5 kcal mol^{-1}, respectively, are the energies required to break the intramolecular hydrogen bond. These are gas-phase values for isolated molecules.

Discussion

Hydrogen Atom Abstraction from *o*-Methoxyphenols. From the previously determined $\Delta H_{\text{intra-HB}}$ of −4.3 kcal mol^{-1} for various *o*-methoxyphenols,[5] it can be calculated that in a non-HBA solvent such as a saturated hydrocarbon at 298 K less than 0.1% of the phenol exists in the non-hydrogen-bonded form.[5] A Hammett correlation for hydrogen atom abstraction by alkoxyl radicals from several para-substituted phenols in CCl_4 gave the following correlation: $\log k_4 = -0.37\Sigma\sigma^+ + 9.12$ with $r^2 = 0.89$,[19] the slope of this plot is solvent dependent. By using the substituent constant for the *o*-methoxy group, the expected rate constant for hydrogen atom abstraction from "free" 2-methoxyphenol is estimated to be 2.0×10^9 M^{-1} s^{-1}.[22] When hydrogen atom abstraction is only possible from this form, 0.1% of "free" 2-methoxyphenol in solution would result in an observed rate constant of 2.0×10^6 M^{-1} s^{-1}. The much higher experimental rate constant in CCl_4 of 9.3×10^7 M^{-1} s^{-1} can only be interpreted by a direct hydrogen atom abstraction from the intramolecularly hydrogen-bonded form. The experimental rate constant is also a factor of 20 lower than the derived value for "free" 2-methoxyphenol, which corresponds to a difference in Gibbs energy of activation of $\Delta\Delta G^{\ddagger}_{298} = 1.8$ kcal mol^{-1}, in perfect agreement with the DFT result. For the electron-rich ubiquinol-0, the calculated value of k_4 for the hypothetical "free" form (present at less than 0.1%) would be 10×10^9 M^{-1} s^{-1},[22] only a factor 4 faster than the experimental value in CCl_4 of 2.8×10^9 M^{-1} s^{-1}. As a result, the contribution of hydrogen atom abstraction from the non-hydrogen-bonded form, if present, to the overall rate constant becomes even smaller when more electron-donating substituents are attached to the aromatic ring.

Apparently the nonlinearity of the intramolecular hydrogen bond leaves the phenolic hydrogen atom available for abstraction, in contrast with the situation for linear intermolecularly hydrogen-bonded phenols.

That phenolic hydrogen atoms involved in intramolecular hydrogen bonds can, indeed, be abstracted is further borne out by the high reactivity of 2,6-dimethoxyphenol toward alkoxyl radicals (see Table 1) since there can be no non-hydrogen-bonded form of this phenol.

The substituent effect on the hydrogen atom abstraction for *o*-methoxyphenols is more pronounced relative to other (non-hydrogen bonded) phenols. For the phenols substituted at the para position the difference in rate constants is relatively small. Substitution at the ortho or para position of 2-methoxyphenol by methoxy groups causes a relatively larger acceleration of the reaction rate. A Hammett plot of the rate constants obtained in CCl_4 for the *o*-methoxyphenols gave the following correlation: $\log k_4 = -1.39\Sigma\sigma^+ + 7.15$ with $r^2 = 0.95$,[24] a much larger slope ρ than in the case of the non-hydrogen bonded phenols with $\rho = -0.37$. Also, the slope is independent of the solvent, which is a direct consequence of the identical solvent effect shown by all investigated *o*-methoxyphenols (see below).

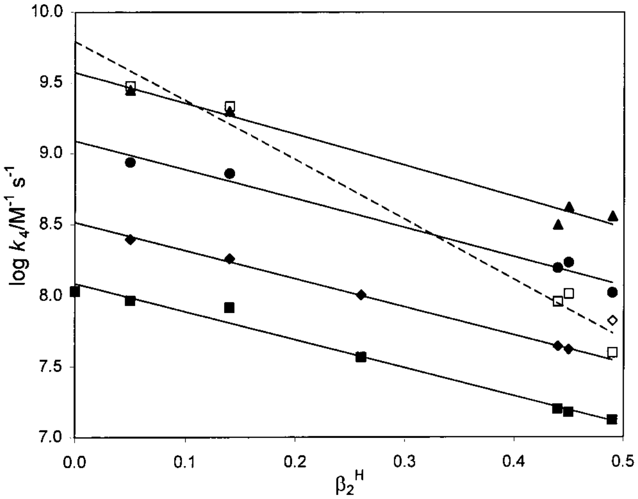


Figure 3. Solvent effect on the kinetics of hydrogen abstraction from (poly)methoxy phenols: (□) 4-methoxyphenol (dashed line), (▲) ubiquinol-0, (●) 2,4-dimethoxyphenol, (◆) 2,6-dimethoxyphenol, and (■) 2-methoxyphenol; (◇) 2,6-dimethoxyphenol in *tert*-butyl alcohol was not used in the linear fit.

Solvent Effect on Hydrogen Atom Abstraction from (MeO)$_x$PhOH. The solute basicity parameter, β_2^{H}, is a measure of the ability of a compound to accept hydrogen bonds.[8] The β_2^{H} values are based on the equilibrium constant for hydrogen-bond formation between a donor and an acceptor in dilute solutions in CCl_4, but are applicable also in the pure HBA solvents because only 1:1 complexes between the phenol and the solvent molecules are formed. It has been found that for the abstraction of the hydroxylic hydrogen atom from phenol, α-tocopherol, and *tert*-butyl hydroperoxide, plots of log *k* vs β_2^{H} are linear.[10] The same kind of plots are shown for the investigated methoxyphenols in Figure 3, where for 4-methoxyphenol, 2,4-dimethoxyphenol, and ubiquinol-0 the recalculated values for the pure solvent are used. The slopes of the straight lines are a measure of the kinetic solvent effect: a stronger interaction between the phenol and the solvent leaves less "free" phenol available for hydrogen atom abstraction, and hence the measured reaction rate decreases. The fact that intramolecularly hydrogen-bonded phenols still exhibit kinetic solvent effects implies that an additional, i.e., intermolecular, hydrogen bond can be formed between the intramolecularly hydrogen-bonded molecule and the HBA solvent. Such an entity, in which the hydrogen atom interacts with three different neighboring atoms, has in several studies been shown to exist in crystal structures[25]

---

(18) The DFT calculations on 2-methoxyphenol show that on formation of the intramolecular hydrogen bond the positive (Mulliken) charge on this hydrogen increases slightly, from 0.315 to 0.331, consequently the rate for reaction with the electrophilic alkoxyl radical may decrease.

(19) A plot of $\log(k_4/\mathrm{M}^{-1}\,\mathrm{s}^{-1})$ vs $\Sigma\sigma^+$ with the rate constants (M^{-1} s^{-1}) for phenol (8.6×10^8,[4] $\sigma^+ = 0$), α-tocopherol (4.2×10^9,[4] $\Sigma\sigma^+ = -1.40$), 4-MeO-PhOH (3.0×10^9 (this work), $\sigma^+ = -0.78$), 4-CF_3-PhOH (7.1×10^8,[10] $\sigma^+ = 0.61$), 4-Me_3C-PhOH (1.9×10^9,[10] $\sigma^+ = -0.26$), 4-Cl-PhOH (1.09×10^9,[10] $\sigma^+ = 0.11$), and 3,5-Cl_2-PhOH (8.8×10^8,[10] $\Sigma\sigma^+ = 0.80$) with CCl_4 as the solvent gave the following correlation: $\log k_4 = -0.37\Sigma\sigma^+ + 9.12$ with $r^2 = 0.89$; σ_p^+ values from ref 20, σ_m^+ values from ref 21.

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

(21) March J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; McGraw-Hill Inc.: New York, 1968; p 241

(22) Taking $\sigma_o^+ = 0.66\sigma_p^+$, a correlation found in several experimental studies,[6, 23] the σ_o^+ for an *o*-methoxy group would be −0.51, implying that the rate constant for nonintramolecularly hydrogen-bonded 2-methoxyphenol would be 2.0×10^9 M^{-1} s^{-1}. For ubiquinol-0 the same procedure gives $\Sigma\sigma^+ = -1.58$ and k_4 for "free" ubiquinol of 5.0×10^9 M^{-1} s^{-1}. Assuming that both OH groups are equivalent, the overall rate would be 10×10^9 M^{-1} s^{-1}.

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

(24) A plot of $\log(k_4/\mathrm{M}^{-1}\,\mathrm{s}^{-1})$ vs $\Sigma\sigma^+$ with the rate constants in CCl_4 from Table 1 and $\Sigma\sigma^+$ for 2-MeO-PhOH (−0.51), 2,6-$(MeO)_2$-PhOH (−1.03), 2,4-$(MeO)_2$-PhOH (−1.29,) and ubiquinol-0 (−1.58) gave the correlation $\log k_4 = -1.39\Sigma\sigma^+ + 7.15$ with $r^2 = 0.95$; σ_p^+ and σ_o^+ values from ref 20, σ_m^+ values from ref 21.

Table 3. Equilibrium Constants for Intermolecular Hydrogen Bonding of Methoxy-Substituted Phenols with Various Solvents[a]

	2-MeO[b]	2-MeO[c]	2,6-$(MeO)_2$[c]	2,4-$(MeO)_2$[c]	ubiquinol-0[c]	4-MeO[c]
tetrachloromethane	0.02					
benzene	0.03	0.01	0.03	0.02	0.04	0.03
acetonitrile	0.30	0.25	0.24	0.24	0.41	1.7
ethyl acetate	0.61	0.51	0.49	0.40	0.56	2.7
tert-butyl alcohol	0.71	0.60	0.27	0.68	0.64	7.0

[a] $K_{\text{inter-HB}}$ in M^{-1} (error approximately ±15%), calculated with eq 5 with the solvent concentration as used in the LFP experiment: The neat liquid when dicumyl peroxide was used or 70 vol % when di-*tert*-butyl peroxide was used. $K_{\text{inter-HB}}$ values derived this way are apparent values because solvent concentrations are used instead of activities. [b] Calculated with respect to the rate constant in pentane. [c] Calculated with respect to the rate constants in CCl_4.

and in solution.[26] It seems reasonable to assume that the abstraction of doubly hydrogen bonded phenolic hydrogen atoms does not occur.

The slopes of the $\log(k_4/M^{-1}s^{-1})$ vs β_2^H lines in Figure 3 for the three *o*-methoxyphenols and ubiquinol-0 are equal and, hence, the fraction of available phenolic compound for hydrogen atom abstraction is the same (kinetic solvent effect).[27] The slope of ca. −2.0 is significantly smaller than the slope for 4-methoxyphenol (−4.2) and phenol (−5.2),[28] which is reasonable since a hydroxyl group already firmly involved in an intramolecular hydrogen bond can be only a poor hydrogen bond donor to a HBA solvent.

Equilibrium Constants for Intermolecular Hydrogen Bonding. From the rate constants measured in different solvents, the equilibrium constants for intermolecular hydrogen bonding with the solvent can be calculated with the aid of eq 5.[2,3,29] For 2-methoxyphenol $K'_{\text{inter-HB}}$ (see Scheme 1) was calculated with respect to the rate constant measured in pentane, a non-HBA solvent. For the other phenols measurements in pentane were not possible due to low solubility, instead the equilibrium constants were calculated with respect to the rate constant measured in the poor HBA solvent CCl_4, for comparison the $K'_{\text{inter-HB}}$ values for 2-methoxyphenol were also calculated this way (Table 3). For the ortho-substituted phenols this is the equilibrium constant for the formation of the additional hydrogen bond of the intramolecularly hydrogen-bonded molecule with the solvent.[30]

$$k_4^{CCl_4} = k_4^S(1 + K^S_{\text{inter-HB}}[S]) \tag{5}$$

The $K'_{\text{inter-HB}}$ values in one solvent are very similar for all *o*-methoxyphenols, see Table 3, and will be close to the $K'_{\text{inter-HB}}$ for 2-methoxyphenol calculated with respect to pentane. The equilibrium constant of around 0.6 M^{-1} for the intermolecular hydrogen bonding of *o*-methoxyphenols with ethyl acetate results in an enthalpy for this hydrogen bond of −2.9 kcal mol^{-1}.[32] As expected, $\Delta H_{\text{inter-HB}}$ for the additional hydrogen bond is lower than the value for 4-methoxyphenol and ethyl acetate of −4.5 kcal mol^{-1} as measured by photoacoustic calorimetry.[5,33] For the other solvents, $\Delta H_{\text{inter-HB}}$ for hydrogen-bond formation with the *o*-methoxyphenols becomes ca. 1.0 kcal mol^{-1} for benzene ($K'_{\text{inter-HB}}$ ca. 0.03 M^{-1}), −2.5 kcal mol^{-1} for acetonitrile ($K'_{\text{inter-HB}}$ ca. 0.3 M^{-1}), and −3.0 kcal mol^{-1} for *tert*-butyl alcohol ($K'_{\text{inter-HB}}$ ca. 0.7 M^{-1}).

Ubiquinol and α-Tocopherol. Ubiquinol-0 has been shown to possess the same hydrogen-bonding properties as the other *o*-methoxyphenols studied. Exactly the same behavior is expected for ubiquinol-10, the natural antioxidant present in human LDL. The two phenolic groups will be hydrogen bonded to their adjacent methoxy groups, thus preventing the formation of strong hydrogen bonds with solvent molecules or polar solutes. In this way, part of the phenolic hydrogen atoms remain available for hydrogen atom abstraction even in a strong HBA environment. This is important in the LDL particle where ubiquinol together with α-tocopherol perform their antioxidant function. The LDL particle is not homogeneous and consists of a core of neutral lipids and a coat of polar lipids,[1] capable of accepting hydrogen bonds.

The rate constant for hydrogen atom abstraction from α-tocopherol by *tert*-butoxyl radical in tetrachloromethane is 4.2×10^9 M^{-1} s^{-1},[4] close to our value for ubiquinol-0 of 2.8×10^9 M^{-1} s^{-1} in the same solvent. This is in agreement with the small difference in BDE(O−H) for both compounds, 77.3 kcal mol^{-1} for α-tocopherol[6] and 78.5 kcal mol^{-1} for ubiquinol-0[5] (the latter value includes the enthalpy involved in breaking the intramolecular hydrogen bond). In HBA solvents, however, α-tocopherol is not protected against strong solvent interactions and in ethyl acetate k_4 decreases to 2.9×10^8 M^{-1} s^{-1},[4] a factor of 2 lower than the 5.6×10^8 M^{-1} s^{-1} found for ubiquinol-0 (Table 1).

The same differences in kinetic solvent effects have been found in antioxidant studies: In a non-HBA environment, ubiquinol-10 is about 10 times less reactive than α-tocopherol toward peroxyl radicals.[34] In aqueous lipid dispersions, however, both compounds show equal antioxidant activity.[35] In the polar environment the rate of hydrogen atom abstraction from

---

(25) (a) Jerslev, B.; Larsen, S. *Acta Chem. Scand.* **1991**, *45*, 285−91. (b) Stomberg, R.; Hauteville, M.; Lundquist, K. *Acta Chem. Scand.* **1988**, *B42*, 697−707. (c) Velavan, R.; Sureshkumar, P.; Sivakumar, K.; Natarajan, S. *Acta Crystallogr.* **1995,** *C51*, 1131−3.

(26) Bureiko, S. F.; Golubev, N. S.; Pihlaja, K. *J. Mol. Struct.* **1999**, *480*−*481*, 297−301.

(27) The observed rate constant for 2,6-dimethoxyphenol in *tert*-butyl alcohol is higher than could be expected from the hydrogen bond accepting properties of the solvent. This may be caused by steric hindrance to the formation of the intermolecular hydrogen bond.

(28) Data from refs 3 and 4.

(29) Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1996**, *118*, 8, 6790−1. Correction: Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1996**, *118*, 12485.

(30) The equilibrium constant derived for 4-methoxyphenol and acetonitrile of 1.7 M^{-1} is low compared to 3.7 M^{-1} measured by infrared spectroscopy.[31] This appears to be a general phenomenon: equilibrium constants derived by kinetic methods have been found to be lower than those obtained by the IR method.[29] Also, from our photoacoustic calorimetric value for $\Delta H_{\text{inter-HB}}$ for 4-methoxyphenol and ethyl acetate of 4.5 kcal mol^{-1},[5] the equilibrium constant would be 9 M^{-1}, again significantly higher than the 2.7 M^{-1} from the kinetic results.

(31) Jawed, I. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2602−5.

(32) Using $\Delta S_{\text{inter-HB}} = 10.7$ cal mol^{-1} K^{-1} derived for hydrogen bonding of 2-methoxyphenol with ethyl acetate.[5]

(33) Intermolecularly hydrogen bonded complexes of the two forms of 2-methoxyphenol with formaldehyde (as model for ethyl acetate) were also calculated by DFT, resulting in $\Delta H_{\text{inter-HB}}$ of −4.1 kcal mol^{-1} for the intramolecularly hydrogen bonded form and −5.9 kcal mol^{-1} for the non-hydrogen bonded form. The difference of 1.8 kcal mol^{-1} is comparable to the difference of 1.6 kcal mol^{-1} for the experimental intermolecular hydrogen bond enthalpies of 2-methoxyphenol and 4-methoxyphenol with ethyl acetate.

(34) Barclay, L. R. C.; Vinqvist, M. R.; Mukai, K.; Itoh, S.; Morimoto, H. *J. Org. Chem.* **1993**, *58*, 7416−20.

(35) Ingold, K. U.; Bowry, V. W.; Stocker, R.; Walling, C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 45−9.

α-tocopherol has decreased more, caused by the stronger hydrogen-bonding interactions, than for ubiquinol-10, which is protected against these strong interactions.

Conclusions

A phenolic hydrogen can form a linear intermolecular hydrogen bond with a particular solvent. Hydrogen atom abstraction from this complex by free radicals does not take place. Upon increasing the hydrogen-bonding capability of the solvent, the amount of available phenol diminishes (kinetic solvent effect). With a hydrogen bond accepting substitutent, such as methoxy, at the ortho position, the phenolic hydrogen is almost exclusively involved in nonlinear intramolecular hydrogen bonding. Hydrogen atom abstraction from this entity remains feasible. The rate constant is lower relative to the (hypothetical) non-hydrogen bonded phenol, since the transition state now pertains to the rupture of a covalent O−H bond and a hydrogen bond in a synchronized fashion. A smaller kinetic solvent effect is present for intramolecularly hydrogen-bonded phenols. Thus, the relative effectiveness in LDL particles of the antioxidants α-tocopherol and ubiquinol (an intramolecularly hydrogen-bonded phenol) will depend on the hydrogen-bonding capability of the microenvironment.

Experimental Section

The laser flash photolysis (LFP) equipment has been described previously.[36] Alkoxyl radicals were generated by photolysis of solutions containing 30 vol % di-*tert*-butyl peroxide at 337 nm or 0.13 M dicumyl peroxide at 308 nm. The optical densities of the solutions were 0.3 at the applied laser wavelength. The LFP experiments (4 to 8 laser shots) were performed in 7 mm quartz cuvettes, and solutions were thoroughly deoxygenated by purging with nitrogen for 5 min prior to photolysis. Second-order rate constants were calculated by least-squares fitting of the experimental pseudo-first-order rate constants vs the phenol concentration, using at least five different concentrations.

4-Methoxyphenol, 2,4-dimethoxyphenol, and ubiquinol-0 kinetics were measured with di-*tert*-butyl peroxide, since these phenols have a strong absorption at 308 nm. The growth of the phenoxyl radical was monitored directly at 410 (4-methoxyphenol), 408 (2,4-dimethoxyphenol), or 430 nm (ubiquinol-0).

The kinetics for 2-methoxyphenol and 2,6-dimethoxyphenol were measured using dicumyl peroxide and monitoring the decay of the cumyloxyl radical at 485 nm.[37] For these compounds, the phenoxyl radicals could not be monitored directly due to their very low extinction coefficients.

Materials. 2-Methoxyphenol was twice distilled under vacuum, 4-methoxyphenol and 2,6-dimethoxyphenol were sublimed twice, dicumyl peroxide was recrystallized from methanol, and di-*tert*-butyl peroxide was passed over alumina prior to use.

2,4-Dimethoxyphenol and 2,4,6-trimethoxyphenol were synthesized following a literature procedure[38] from the corresponding benzaldehydes, and were further purified by sublimation. Ubiquinol-0 was obtained by reduction of ubiquinone-0 with $Na_2S_2O_4$.

Solvents were of the highest purity available and were used without further purification, except for anisole which was purified by extraction with 2 M NaOH followed by washing with water to remove phenolic impurities and distillation from chips of sodium metal. When *tert*-butyl alcohol was used with dicumyl peroxide, 5% benzene was added to the solvent.

Computational Procedures. Density functional theory (DFT) calculations were performed with the Gaussian 94 suite of programs[39] on an IBM RS/6000 computer. Geometries of ground and transition states were fully optimized to stationary points on the (U)B3LYP level using the 6-31G(d,p) basis set. Frequency calculations were performed on the same level of theory. Zero-point vibrational energies (ZPVE) were scaled by a factor of 0.9805.[40]

Acknowledgment. We thank the Hochschulrechenzentrum Essen for generous allotment of computer resources. We also thank the National Foundation for Cancer Research for financial support. One of us (M.I.deH.) thanks The Netherlands Organization for Scientific Research (NWO) for the travel grant and D.W. Snelgrove for technical assistance and useful discussions. We thank Prof. Dr. J. Cornelisse for carefully reading the manuscript.

JA9937674

---

(36) (a) Scaiano, J. C.; Tanner, M.; Weir, D. *J. Am. Chem. Soc.* **1985**, *107*, 4396−4403. (b) Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7747−53.

(37) Avila, D. V.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4, 6576−7.

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

(39) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, W. P. M.; 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.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, 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 94, Revision E.3*; Gaussian, Inc.: Pittsburgh, PA, 1995.

(40) (a) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513. (b) Korth, H.-G.; Sicking, W. *J. Chem. Soc., Perkin Trans. 2* **1997**, 715−19.