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Hydrogen Bonding between Phenols and Fatty Acid Esters: ^{1}H NMR Study and ab Initio Calculations

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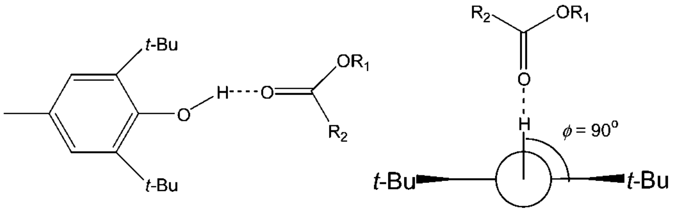
ABSTRACT



^{1}H NMR measurements and ab initio calculations were used to study the interactions between hindered/nonhindered phenols and carboxylic acid esters. The dihedral angle (φ) between the OH group and a plane of the aromatic ring is close to 0° in the hydrogen-bonded nonhindered phenols, whereas for 2,6-di-*tert*-butyl-4-methylphenol the OH group is completely twisted out of the aromatic plane ($\varphi \approx 90°$).

Hydrogen bond (HB) formation is the main factor responsible for kinetic solvent effects (KSE) on the chain-breaking antioxidant activity (AA) of phenols.[1] Interactions between the hydrogen atom of the phenolic hydroxyl group and the solvent reduce the amount of free phenol and the apparent rate constant for hydrogen atom abstraction ($\text{PhOH} + \text{ROO}^{\bullet} \rightarrow \text{PhO}^{\bullet} + \text{ROOH}$) is lower in HB accepting solvents. Diffusional effects within and between micelles and differential partitioning of the phenols between the aqueous and lipid phases[2] together with HB formation cause the AA of phenolic antioxidants to be dramatically reduced in bilayers compared with homogeneous solutions and produce a "leveling effect", i.e., the activities of various classes of antioxidants become rather similar.[2,3]

Recently, Snelgrove et al.[4] gave an empirical formula valid for homogeneous solutions that connects the rate constant for hydrogen atom transfer with properties of solvent (HB basicity) and phenol (HB acidity) and allows the prediction of the KSE for hindered phenols of known values of HB acidity. In nonhomogeneous media the interactions of lipids and phospholipids with phenols will be important but have been largely ignored with many studies having been focused on the structural stability of lipid bilayers containing tocopherols and flavonoids and on the localization of tocopherol in bilayers.[5]

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Because oxygen atoms in carboxylate esters are the main HB acceptors in ester molecule[6] and hydrogen bonding between an ester and phenol is assumed to decrease the AA of nonhindered phenols,[7] we decided to study how steric hindrance of the OH group affects the interactions between phenols and a simple model lipid (ethyl laurate).

Three classes of phenols were chosen: nonhindered phenols, 4-fluorophenol (**1a**) and 4-methylphenol (**1b**); partially hindered phenols substituted at one *ortho*-position, 2-methylphenol (**2a**), 2,4-dimethylphenol (**2b**), 2-isopropyl-5-methylphenol (**2c**); and more hindered phenols substituted at both *ortho*-positions, 2,2,5,7,8-pentamethyl-6-hydroxychroman (PMHC, **3a**), 2,6-dimethylphenol (**3b**), 2,4,6-trimethylphenol (**3c**), 2-*tert*-butyl-6-methylphenol (**3d**), 2,6-di-isopropylphenol (**3e**), and 2,6-di-*tert*-butyl-4-methylphenol (BHT, **3f**). The last two compounds are especially interesting because Franchi et al.[8] and Lucarini et al.[9] described BHT as a molecule that does not form hydrogen bonds even in strong HB acceptors (HB was not detected by the means of IR), and in work of Abraham et al.[10] compounds **3e** and **3f** were excluded from analysis of solute HB acidity.

BHT and other 2,6-di-*tert*-butyl-substituted phenols have been used to measure bond dissociation enthalpies (BDE) for other phenols in an ESR-monitored equilibrium process:[10,11] $\text{PhOH} + 2,6\text{-di-}^t\text{Bu-PhO}^\bullet \rightleftharpoons \text{PhO}^\bullet + 2,6\text{-di-}^t\text{Bu-PhOH}$. As a result of supposed lack of solvation of these hindered phenols, their BDEs should be constant even in the presence of HB accepting solvents. However, the literature is not completely consistent with the inability of these phenols to form HBs, because BHT has been reported to form a HB with several polar solvents[12] and some thermodynamic parameters of HB with ethanol, chloroform, and acetone were determined.[13] Since HB interactions between lipids and phenolic antioxidants have great significance, we decided to use ^{1}H NMR to investigate HB formation between model compounds: fatty acid ester and hindered phenols.[14]

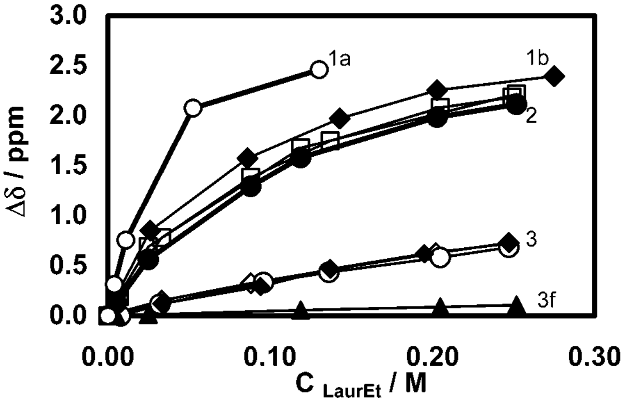

Figure 1. ^{1}HMR chemical shift changes, $\Delta\delta = \delta_{OH}$ (in the presence of ester) $- \delta_{OH}$ (in the absence of ester), of hydrogen from the phenol hydroxyl group in the presence of various concentrations of ethyl laurate. Data presented for 4-F-phenol (**1a**); 4-Me-phenol (**1b**); 2-Me-phenol, 2,4-Me$_2$-phenol, 2-^{i}Pr-5-Me-phenol (denoted as **2**); PMHC, 2,4,6-Me$_3$-phenol, 2-^{t}Bu-6-Me-phenol (denoted as **3**), and BHT (**3f**).

Initially, to avoid self-association of the phenols we investigated the concentrations (C_{PhOH}) at which they are "free" (i.e., nonassociated). No significant changes in the chemical shift of hydrogen atom from hydroxyl group (δ_{OH}) vs. C_{PhOH} were observed below 0.004 M for nonhindered phenols and 0.016 M for phenols **3e** and **3f**; thus the optimal C_{PhOH} in cyclohexane was found as 0.004 M. This value is in good agreement with IR and calorimetric data,[15] and we used this concentration in further measurements.

Plots of chemical shift changes ($\Delta\delta$) as a function of increasing ethyl laurate concentration are shown in Figure 1. The highest $\Delta\delta$ is for a nonhindered phenol with a 4-fluoro substituent, **1a**, and a large effect is also observed for compounds **2a**−**c**. 2,6-Disubstituted phenols **3a**, **3d**, **and 3f** have much smaller $\Delta\delta$, and for the most hindered phenol (**3f**) a weak but detectable increase of $\Delta\delta$ can be observed. Therefore, on the basis of ^{1}HMR data, the presence of HB PhO−H···ester, even for the most hindered phenols **3d**−**f**, was confirmed. To verify that the ester's carboxylic oxygens take part in this interaction, we used ^{17}O NMR, which is a convenient method for determining of HB binding sites.[16] The free ester chemical shifts of oxygen from C═O and O−Et were at 360.5 and 173.2 ppm, respectively, and they are in good agreement with literature data for ester oxygen

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(13) Thermodynamic parameters given in ref 12d for BHT−chloroform complexes are $\Delta H = -1.0 \pm 0.2$ kcal/mol, $\Delta S = -6.2 \pm 0.5$ eu, $K = 0.21 \pm 0.01$ M^{-1}, and for BHT−acetone the parameteres are $\Delta H = -2.4 \pm 0.2$ kcal/mol, $\Delta S = -10.5 \pm 0.5$ eu, $K = 0.35 \pm 0.01$ M^{-1}.

(14) Conditions and equipment: Varian Unity Plus 200, field frequency 200 MHz, the external standard (C_6H_6 "lock"). For ^{17}O NMR measurements: Varian Unity Plus 500, field frequency 500 MHz, 25 °C, 148 608 repetitions, total time 16 h. The field was optimized using D_2O. Solvent: cyclohexane was dried and rectified over metallic sodium, with purity controlled by GC. All investigated phenols (purity 97−99%) were purchased from Sigma-Aldrich, as well as ethyl laurate (99%) and DPPH (97%). Phenols and solvents were stored under nitrogen at 0−5 °C. FT IR, and ^{1}H NMR measurements proved that there was no detectable water in the solvents used.

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Table 1. Calculated Parameters of Phenol−Ester Complexes

phenol	E_{total} (hartree)	$E_{\text{O}\cdots\text{H}}$ (kcal/mol)	$R_{\text{O}\cdots\text{H}}$ (Å)	$R_{\text{O}\cdots\text{O}}$ (Å)	C−O−H interbond (deg)	Ar−O−H dihedral (deg)	O−H···O interbond (deg)
1a[a]	−675.110	8.04	1.819	2.777	111	0.5	163.9
1a[b]	−671.266	7.22	1.947	2.872			164.8
2a	−611.456	6.14	2.021	2.887	114	6.4	151.0
1b	−611.457	6.53	1.966	2.885	111	0.0	162.3
3a	−958.411	5.38	2.014	2.961	111	58.1	175.6
3b	−650.496	5.97	2.028	2.891	114	3.0	150.5
3c	−689.535	5.92	2.027	2.890	113	0.0	150.5
3d	−767.598	5.90	2.039	2.902	113	12.9	150.6
3f	−923.736	5.21	2.044	2.921	112	91.2	153.0

[a] All values calculated by RHF/6-31G**. [b] Obtained by DFT-B3LYP/6-31G** calculations in order to estimate the correlation effect.

atoms.[17] For ester containing 0.5 M **1b** the chemical shifts were smaller (342.5 and 164.8 ppm, respectively) indicating the formation of intermolecular hydrogen bonds. This experiment also demonstrated that both oxygen atoms of the ester take part in HB complexation, but not equally.

Our measurements of abilities of phenols to form hydrogen bonds with esters were further confirmed by ab initio calculations. We have calculated the geometry and energy parameters of phenol−ester complexes using methyl acetate as a model ester. The results are listed in Table 1. The structures of the complexes were optimized by Hartree−Fock calculation (RHF) at the 6-31G** level of theory using the GAUSSIAN 94 program.[18] Optimization led to several conformational structures for each complex and we present the data for those of the lowest energy. For each complex the normal vibration frequencies were calculated and the values of all the force constants were positive, which corroborates that a local minimum had been found. The molecular interaction energy was evaluated by the supermolecule method using a counterpoise correction. The correlation effect was estimated as 10% using DFT/B3LYP/6-31G** calculations.

Results listed in Table 1 confirm the experimental data presented above. Calculated energies of interactions are within the range 5−8 kcal/mol, and they are typical for HB energies of middle strength. It should be noted that both theory (ab initio) and experiment (NMR) indicate that strongly hindered phenols are able to form hydrogen bonds. It is also intriguing to compare the dihedral OH out-of-the aromatic plane angles (φ, see graphical abstract) in the hydrogen-bonded complexes. The O−H group lies in the plane of the aromatic ring for phenol and its *o*-methyl derivatives. Such planar structures have energy minima for φ close to 0° with rotation barriers of about 3.5 kcal/mol.[19] The HB interactions of those phenols with esters are not substantially affected by steric hindrance, and therefore the OH group is not twisted out of the aromatic plane. Even for **3d** the angle φ is 12.9°, i.e., close to the planar structure observed experimentally for the OH group pointing away from the *tert*-butyl groups in 2-*tert*-butylphenol and 2-*tert*-butyl-6-methylphenol in the liquid and gas phases.[12b,20] However, two phenols provide exceptions to this general rule: the α-tocopherol analogue (**3a**) and BHT (**3f**). This is not particularly surprising for **3a** because the ring−OH dihedral angle remains the same as for crystalline non-hydrogen-bonded structure (reported 45−59°).[21] More interesting is the nearly perpendicular OH ($\varphi = 91.2°$) for hydrogen-bonded 2,6-di-*tert*-butyl-4-methylphenol. In this and other 2,6-di-*tert*-butylphenols the noncomplexed OH group lies in the plane of the aromatic ring.[22] The presence of two *o*-*tert*-butyl groups reduces the OH rotational barrier to 2.8 kcal/mol.[23] However, the energy of the hydrogen bond between the ester and phenol (5.2 kcal/mol) exceeds this rotational barrier and causes the OH group to twist 90° out of the aromatic plane on formation of a HB.

The fact that **3a** and **3f** have the lowest BDEs among the phenols studied and that their solvated structures have Ar−O−H dihedral angles far from 0° provides an explanation for relatively fast hydrogen atom abstraction from **3f**. This compound has a surprisingly low BDE despite the absence of a *p*-alkoxy group. In an analysis of BDEs for ring-substituted phenols made by Wayner et al.[24] BHT was excluded from a correlation of BDE vs σ^+ substituent constants because this phenol had a significantly lower BDE than would be predicted solely from the electronic effect of the ring substituents. It was concluded that BHT was destabilized by the presence of two *o*-*tert*-butyl groups.

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Perpendicular conformation of the OH group may be one of the possible explanations of this additional lowering of BDE because of its similarity to conformation of the OH group in phenols containing an ether oxygen in the *para*-position. Reported values of φ for non-hydrogen-bonded PMHC, 2,3,5,6-tetramethyl-4-methoxyphenol, 4-methoxyphenol, and 2,6-di-*tert*-butyl-4-methoxyphenol are 45−59°, 30.9°, 27.3°, and 4.8°, respectively.[21] Enhanced AA of these *p*-alkoxyphenols is due to delocalization of the unpaired electron of the corresponding phenoxyl radicals onto the p-type lone pair of the methoxyl oxygen in position 4.[15] Optimal orientation of this lone pair with respect to the aromatic plane would be perpendicular (90°), but even for the best antioxidants in this class, this angle is 82° to 60° for steric reasons. For such phenols a twisted OH will be favored in the process of abstraction of the phenolic hydrogen in order to obtain resonance stabilization by delocalization of the developing unpaired electron onto the aromatic π system.[25] The angle φ in PMHC (**3a**) is twisted in both free and hydrogen-bonded compounds, whereas in 2,6-di-*tert*-butyl phenols the φ is twisted as a result of hydrogen bond. Thus, both H-bonded structures have similar conformations of Ar−O−H and the low BDE is observed for **3a** (78.3 kcal/mol) and **3f** (81.0 kcal/mol) in comparison with nonhindered phenols (up to 88.3 kcal/mol for phenol itself). In other words, increasing φ in H-bonded phenol can decrease the bond strength as a result of lack of conjugation of the oxygen p-orbital lone pair with benzene π electrons.

The conjugation is possible after a cleavage of HB (and the OH group will come back to the coplanar structure) or after a cleavage of the O−H bond to give an unpaired electron for conjugation with benzene π electrons. Thus, if hydrogen bond phenol···peroxyradical is assumed as pre-transition state[26] for hydrogen atom transfer (HAT), the twisted OH bond in **3f** requires less energy to be broken. Some of the parameters calculated for hydrogen bonded structures in this work are similar to those calculated by de Heer et al.[27] for the transition state for HAT from 2-methoxyphenol (with and without an internal HB) by the methoxyl radical (the interbond O−H···O angle is 162.4° and φ is 25°).[27] Although the above values indicate a striking similarity of the studied HB complexes' geometry to the transition state structures of HAT by oxygen-centered radicals, detailed considerations[26a] indicated that only a small number of HB phenol···peroxy radical structures may be converted into the transition state since only a small Arrhenius preexponential factor is observed for HAT between phenols and oxygen-centered radicals.[28] Assuming that the transition state arises from one (effective) HB out of ineffective HBs (which dramatically decrease the reactivity of phenols), the low energies of HBs calculated for PHMC and BHT in comparison with other phenols may be advantageous, since such ineffective phenol···radical complexes will be relative easily dissociated. 1−2 kcal/mol differences observed between energies of HBs formed by nonhindered and hindered phenols are sufficient to make the values of $\Delta\delta$ noticeably smaller (Figure 1). This agrees with the significantly lower HB equilibrium constants reported for a small decrease of thermodynamic parameters for other phenol−solvent systems.[12c,d,13,15]

In conclusion, our experiments and calculations prove that the strength of the HB between the phenolic hydroxyl group and oxygen from an ester carboxyl group is dependent on steric hindrance. Even for sterically crowded phenols this interaction is detectable and possible because, in the hydrogen-bonded 2,6-di-*tert*-butylated phenols, the orientation of OH group is perpendicular to the aromatic plane.

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[28] In "normal" HB the lone electron pair of oxygen is involved, whereas in the hypothetical H-bonded transition state an orbital with an unpaired electron must take part. Probabillity of this structure is much lower.[26a]