Hydrogen-Bonding Effects on the Properties of Phenoxyl Radicals. An EPR, Kinetic, and Computational Study

Marco Lucarini,*,† Veronica Mugnaini,† Gian Franco Pedulli,*,† and
Maurizio Guerra*,‡

*Contribution from the Dipartimento di Chimica Organica "A. Mangini", Università di Bologna,
Via S. Donato 15, I-40127 Bologna, Italy, and I.S.O.F., Consiglio Nazionale delle Ricerche,
Via P. Gobetti 101, I-40129 Bologna, Italy*

Received March 3, 2003; E-mail: lucarini@alma.unibo.it; guerra@isof.cnr.it

Abstract: The effect of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP) on the properties of phenoxyl radicals has been investigated. HFP produces large variations of the phenoxyl hyperfine splitting constants indicative of a large redistribution of electron spin density, which can be accounted for by the increased importance of the mesomeric structures with electric charge separation. The conformational rigidity of phenoxyl radicals with electron-releasing substituents is also greatly enhanced in the presence of HFP, as demonstrated by the 2 kcal/mol increase in the activation energy for the internal rotation of the *p*-OMe group in the *p*-methoxyphenoxyl radical. By using the EPR equilibration technique, we have found that in phenols the O−H bond dissociation enthalpy (BDE) is lowered in the presence of HFP because it preferentially stabilizes the phenoxyl radical. In phenols containing groups such as OR that are acceptors of H-bonds, the interaction between HFP and the substituent is stronger in the phenol than in the corresponding phenoxyl radical because the radical oxygen behaves as an electron-withdrawing group, which decreases the complexating ability of the substituent. In phenols containing OH or NH_2 groups, EPR experiments performed in H-bond accepting solvents showed that the interaction between the solvent and the substituent is much stronger in the phenoxyl radical than in the parent phenol because of the electron-withdrawing effect of the radical oxygen, which makes more acidic, and therefore more available to give H-bonds, the OH or NH_2 groups. These experimental results have been confirmed by DFT calculations. The effect of HFP solvent on the reactivity of phenols toward alkyl radicals has also been investigated. The results indicated that the decrease of BDE observed in the presence of HFP is not accompanied by a larger reactivity. The origin of this unexpected behavior has been shown by DFT computations. Finally, a remarkable increase in the persistency of the α-tocopheroxyl radical has been observed in the presence of HFP.

Introduction

The conversion of a phenol to a phenoxyl radical is of considerable interest in a variety of biological and technological processes including reduction of ribonucleotides,[1] tyrosyl radical-mediated damage of proteins,[2] production and utilization of oxygen in photosystem II,[3] and antioxidant activity of vitamin E and related phenols.[4]

The ability of phenoxyl radicals to accept hydrogen bonds from hydrogen bond donors (HBD) is believed to be important in changing their properties. EPR and computational studies have shown that hydrogen bonding may have a stabilizing effect for tyrosyl radicals in several enzymes.[2,5] Hydrogen bond formation by tyrosyl radicals has also been suggested to play a key role

in catalyzing cytosine−tyrosine cross-linking in DNA damage.[2] Hydrogen bonding between tyrosyl radicals and a properly oriented protonated histidine residue has also been found to regulate the redox behavior of the tyrosine/tyrosyl radical couple.[5,6] A model compound that allows the reversible electron transfer between phenol and a phenoxyl radical with the assistance of hydrogen bonding has recently been reported.[7]

Computational evidence has been obtained by DFT calculations that the phenoxyl/phenol hydrogen atom self-exchange reaction can be regarded as a proton-coupled electron transfer.

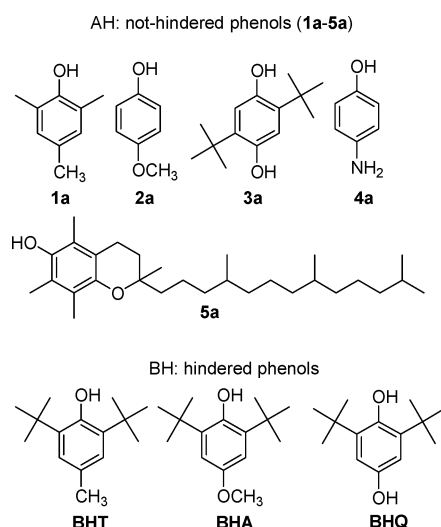† Università di Bologna.
‡ I.S.O.F.
(1) (a) Sjödin, M.; Styring, S.; Åkermark, B.; Sun, L.; Hammarström, L. *J. Am. Chem. Soc.* **2000**, *122*, 3932−3936. (b) Stubbe, J. A.; van der Donk, W. A. *Chem. Rev.* **1998**, *98*, 705−762. (c) Siegbahn, P. E. M.; Eriksson, L.; Himo, F.; Pavlov, M. *J. Phys. Chem. B* **1998**, *102*, 10622−10629. (d) Siegbahn, P. E. M.; Blomberg, M. R. A.; Crabtree, R. H. *Theor. Chem. Acc.* **1997**, *97*, 289−300.
(2) Ban, F.; Lundqvist, M. J.; Boyd, R. J.; Eriksson, L. A. *J. Am. Chem. Soc.* **2002**, *124*, 2753−2761.

(3) (a) Campbell, K. A.; Peloquin, J. M.; Diner, B. A.; Tang, X.-S.; Chisolm, D. A.; Britt, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 4787−4788. (b) O'Malley, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 11732−11737. (c) Tommos, C.; Babcock, G. T. *Acc. Chem. Res.* **1998**, *31*, 18−25. (d) Proshlyakov, D. A.; Pressler, M. A.; DeMaso, C.; Leykam, J. F.; DeWitt, D. L.; Babcock, G. T. *Science* **2000**, *290*, 1588−1591. (e) Maki, T.; Araki, Y.; Ishida, Y.; Onomura, O.; Matsumura, Y. *J. Am. Chem. Soc.* **2001**, *123*, 3371−3372.
(4) (a) Burton, G. W.; Joyce, A.; Ingold, K. U. *Arch. Biochem. Biophys.* **1982**, *221*, 281−290. (b) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, I.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053−7065. (c) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194−201.
(5) (a) van Dam, P. J.; Willems, J.-P.; Schmidt, P. P.; Pötsch, S.; Barra, A.-L.; Hagen, W. R.; Hoffman, B. M.; Andersson, K. K.; Gräslund, A. *J. Am. Chem. Soc.* **1998**, *120*, 5080−5085. (b) Engström, M.; Himo, F.; Gräslund, A.; Minaev., B.; Vahtras, O.; Agren, H. *J. Phys. Chem. A* **2000**, *104*, 5149−5153.

Scheme 1

AH: not-hindered phenols (**1a–5a**)

1a   **2a**   **3a**   **4a**

5a

BH: hindered phenols

BHT   **BHA**   **BHQ**

This mechanism requires the formation of a hydrogen bond and therefore cannot operate in self-exchange reactions similar to those in the benzyl/toluene hydrogen exchange.[8]

The stabilization of the semiquinone radicals derived from catechols, due to intramolecular hydrogen bonding, is considered to be the main effect controlling the excellent behavior of natural catechols as antioxidants.[9]

Finally, several DFT computational studies have shown that the capability of phenoxyl radicals to accept hydrogen bonds from hydrogen bond donors (HBD) is important in changing their EPR spectroscopic properties.[10]

Despite the large interest concerning the effects of hydrogen bonding on the properties of phenoxyl radicals, no quantitative studies of such effects have been reported so far. Here we present an EPR investigation carried out to provide a quantitative description of the factors governing the formation of hydrogen bonding in phenoxyl radicals and of the effects of this interaction on their physical and chemical properties. A density functional theory (DFT) study is also reported, which allows a better rationalization of the experimental thermodynamic and kinetic results.

We have investigated the series of phenols shown in Scheme 1. Some of them are sterically unhindered in the proximity of the OH group and therefore should give rise to phenoxyl radicals easily complexed by HBD solvents. Some others, containing *tert*-butyl groups in both *ortho* positions, are expected to give

phenoxyl radicals experiencing small or negligible interactions at the radical oxygen with HB donors. Actually, in the case of hydrogen bond acceptor (HBA) solvents, the absence of hydrogen bonding to the OH group of 2,6-di-*tert*-butyl phenols was demonstrated by the observation in the 3200–3800 cm^{-1} region of their FT-IR spectrum of only the peak due to the free OH group both in isooctane and in γ-valerolactone, that is, in a very poor and in a strong HBA solvent.[11] Moreover, the absolute rate constants for the reaction of alkyl radicals with 2,6-di-*tert*-butylphenol in toluene and γ-valerolactone showed a negligible kinetic solvent effect, this indicating that hydrogen bond formation is unimportant.[11,12] Experimental evidence supporting the absence of hydrogen-bonding interactions of the phenoxyl radicals from the 2,6-di-*tert*-butyl substituted phenols of Scheme 1 with HBD solvents will be discussed later in the paper.[13]

The effect of a HBD solvent was investigated using a fluorinated alcohol such as 1,1,1,3,3,3-hexafluoropropan-2-ol (HFP), characterized by a large α_2^H value (0.771) indicative of an extremely strong hydrogen bond donor character, and by a β_2^H value very close to zero (0.03),[14,15] implying that no interaction should occur with the hydrogen of OH or NH$_2$ groups.

Results and Discussion

HB-Effects on the hfs Constants of Phenoxyl Radicals. The phenoxyl radicals were generated within the cavity of an EPR spectrometer, by continuous UV irradiation of deoxygenated di-*tert*-butyl peroxide/benzene solutions of one of the phenols shown in Scheme 1, either in the absence or in the presence of HFP. With a few representative phenols, spectra were also recorded by using acetonitrile (ACN) or ethyl acetate as solvents to show the effects of HB acceptors on the hyperfine splitting (hfs) constants (see Table 1). An examination of this table shows that the solvent dependence of the proton splittings is moderate in the phenoxyl radicals from the three 2,6-di-*tert*-butyl substituted phenols BHT, BHA, and BHQ,[16] suggesting that hydrogen bonding at the radical oxygen is unimportant. On the other hand, the spectral parameters of the radicals from the five unhindered phenols of Scheme 1 experience a very big

(6) (a) Uhlin, U.; Eklund, H. *Nature* **1994**, *370*, 533–539. (b) Nordlund, P.; Eklund, H. *J. Mol. Biol.* **1993**, *232*, 123–164. (c) Sjoberg, B.-M. *Structure* **1994**, *2*, 793–796. (d) Siegbahn, P. E. M.; Blomberg, M. R. A.; Crabtree, R. H. *Theor. Chem. Acc.* **1997**, *97*, 289–300. (e) Rova, U.; Goodtzova, K.; Ingemarson, R.; Behravan, G.; Gräslund, A.; Thelander, L. *Biochemistry* **1995**, *34*, 4267–4275. (f) Schmidt, P. P.; Rova, U.; Thelander, L.; Gräslund, A. *J. Biol. Chem.* **1998**, *273*, 21463–21472. (g) Un, S.; Atta, M.; Fontecave, M.; Rutheford, A. W. *J. Am. Chem. Soc.* **1995**, *117*, 10713–10719. (h) Fang, Y.; Liu, L.; Feng, Y.; Li, X.-S.; Guo, Q.-X. *J. Phys. Chem. A* **2002**, *106*, 4669–4678.
(7) Maki, T.; Araki, Y.; Ishida, Y.; Onomura, O.; Matsumura, Y. *J. Am. Chem. Soc.* **2001**, *123*, 3371–3372.
(8) (a) Mayer, J. M.; Hrovat, D. A.; Thomas, J. L.; Borden, W. T. *J. Am. Chem. Soc.* **2002**, *124*, 11142–11147. (b) Kirby, J. P.; Roberts, J. A.; Nocera, D. G. *J. Am. Chem. Soc.* **1997**, *119*, 9230–9236.
(9) (a) Barclay, L. R. C.; Edwards, C. E.; Vinqvist, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 6226–6231. (b) Lucarini, M.; Pedulli, G. F.; Mugnaini, V. *J. Org. Chem.* **2002**, *67*, 928–931.
(10) (a) O'Malley, P. J. *J. Phys. Chem. A* **1998**, *102*, 248–253. (b) Chipman, D. M. *J. Phys. Chem. A* **1999**, *103*, 11181–11187. (c) Chipman, D. M. *J. Phys. Chem. A* **2000**, *104*, 11816–11821. (d) Langella, E.; Improta, R.; Barone, V. *J. Am. Chem. Soc.* **2002**, *124*, 11531–11540.
(11) Franchi, P.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L.; Lunelli, B. *J. Am. Chem. Soc.* **1999**, *121*, 507–514.
(12) (a) Ingold, K. U. *Can. J. Chem.* **1960**, *38*, 1092–8. (b) Ingold, K. U.; Taylor, D. R. *Can. J. Chem.* **1961**, *39*, 481–7. (c) Ingold, K. U.; Taylor, D. R. *Can. J. Chem.* **1961**, *39*, 471–80.
(13) Very recently, it has been reported that in sterically crowded 2,6-di-*tert*-butylated phenols a small interaction between the phenolic hydroxyl group and HBA molecule is possible only when the orientation of the OH group is perpendicular to the aromatic plane. Litwinienko, G.; Megiel, E.; Wojnicz, M. *Org. Lett.* **2002**, *4*, 2425–2428.
(14) β_2^H and α_2^H represent a general, thermodynamically related scale of solute hydrogen bond basicities and acidities in CCl$_4$, respectively. β_2^H values range in magnitude from 0.00 for a non HBA solvent such as an alkane to 1.00 for hexamethylphosphoric triamide (HMPA). Values of α_2^H range from 0.00 (e.g., alkanes) to nearly 1.0 for strong acids (CF$_3$COOH = 0.951). (a) Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Duce, P. P.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 699–710. (b) Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 521–529.
(15) Eberson, L.; Hartshorn, M. P.; Persson, O.; Radner, F. *Chem. Commun.* **1996**, 2105–2111 and references therein.
(16) In the case of BHQ, the EPR spectral parameters of the observed radicals were consistent with the phenoxyl radical centered on the hindered oxygen atom. Actually, the spectrum of the phenoxyl radical showed coupling of the unpaired electron with the two *meta*-protons (0.88 G) and with the remaining hydroxyl proton (1.40 G). The formation of the other possible species, with the radical centered on the oxygen in position 4, can be discarded because larger splittings (ca. 6.5 G) from the protons in 3 and 5 would be expected in this case.

Table 1. Room-Temperature (293 K) Hyperfine Splitting Constants (Gauss = 0.1 mT) for the Investigated Phenoxyl Radicals in Different Solvents and Equilibrium Constants and Free Energy Changes for Reaction 1

		benzene	ACN	CH₃COOEt	benzene/HFP (70:30)	K_1/M^{-1}	$\Delta G_1°/$ kcal mol⁻¹
1a	$a(3H)$	10.89			11.38	21.0 ± 1.8	−1.77
	$a(6H)$	6.33			5.90		
	$a(2H)$	1.71			1.38		
2a	$a(2H)_o$	5.75			4.90	43.6 ± 4.1	−2.20
	$a(2H)_m$	0.80			0.13		
	$a(3H)$	1.78			2.10		
3a	$a(H)_o$	5.22		5.07	4.48	75.2 ± 8.1	−2.51
	$a(H)_m$	0.93		0.83	0.54		
	$a(H)_{OH}$	1.40		1.51	1.73		
4a	$a(2H)$	1.00ᵃ			1.30ᵇ		
	$a(2H)$	3.64ᵃ			3.23ᵇ		
	$a(2H)$	4.68ᵃ			5.00ᵇ		
	$a(N)$	4.68ᵃ			4.97ᵇ		
5a	$a(3H)$	5.92	5.87		5.00	64.2 ± 5.2	−2.42
	$a(3H)$	4.56	4.42		3.47		
	$a(3H)$	0.86	0.77		∼0		
	$a(2H)$	1.44	1.34		0.30		
BHT	$a(3H)$	11.22	11.47	11.33	11.56		
	$a(2H)$	1.67	1.63	1.66	1.51		
BHA	$a(3H)$	1.55	1.62	1.57	1.70		
	$a(2H)$	0.95	0.85	0.92	0.68		
BHQ	$a(H)$	1.40	1.44	1.43	1.54		
	$a(2H)$	0.88	0.80	0.83	0.70		

ᵃ Benzene/*tert*-butyl alcohol 60/40 (v/v). ᵇ Benzene/*tert*-butyl alcohol/HFP 42/28/30 (v/v).

Scheme 2
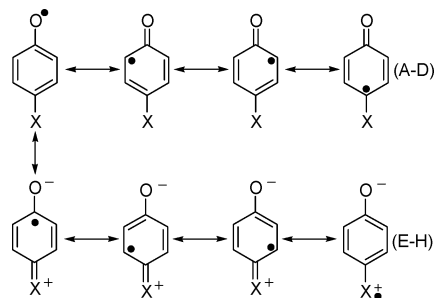
change in the mixture benzene/HFP and only a small variation in ACN or ethyl acetate. The behavior of the radicals from **1a**−**5a** can be explained in both cases in terms of the larger importance in polar solvents of the higher energy mesomeric structures (E−H) involving charge separation (see Scheme 2).

The different magnitude of the solvent effect for HBA and HBD solvents is due to the fact that in the former case the small preference for polar structures is only determined by the increase of the dielectric constant with respect to benzene, while in HFP the specific hydrogen-bonding interaction, strongly stabilizing all structures bringing a negative charge on the oxygen atom, increases significantly the contribution of the structures (E−H) to the mesomeric system.

The decrease of the splittings at the aromatic protons or at the methyl protons in the *ortho* and *meta* positions, observed in HFP, can be explained as follows. These radicals are known to have an odd alternant spin population pattern with large positive spin densities at the oxygen and at the *ortho* and *para* positions and small negative spin densities at the other ring
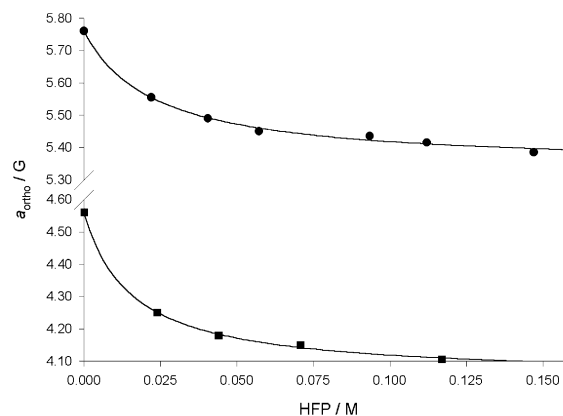
Figure 1. Experimental dependence on the HFP concentration of $a(H)_{ortho}$ for the phenoxyl radical from **2a** (●) and of the smaller of the two $a(CH_3)_{ortho}$ (■) for the radical from **5a**, at 293 K in benzene. The lines represent the theoretical dependence of a_H on the alcohol concentration calculated by taking into account only the formation of hydrogen bonding and were obtained by numerical fitting of the experimental data by using eq 2. K_1 and a_{bound} were determined as adjustable parameters.

positions including the *meta* carbons, consistent with the canonical structures A−D (Scheme 2). In the higher energy polar structures E−H, on the other hand, the expected spin density pattern is complementary to that predicted for structures A−D, that is, positive for the *meta* and *ipso* positions and negative for the positions *ortho* and *para* to the oxygen radical center. The increased solvent polarity and the formation of a hydrogen bond to the oxygen radical center induce a stabilization of the polar structures E−H and opposite spin densities at the *ortho* and *meta* carbons with respect to A−D with a consequent reduction of the hyperfine splittings at the nuclei in these positions.[17] Figure 1 shows, as an example, the experimental dependence on the HFP concentration of the *ortho* hyperfine splittings in the phenoxyl radical derived from **2a** and **5a** in benzene at 293 K.

This dependence is a clear indication of the formation of a hydrogen-bonded complex between phenoxyl radical and HFP. Because the formation and breaking of the hydrogen bonds are fast on the EPR time scale, the experimental spectrum represents the concentration-weighted average of the spectra due to the free and hydrogen-bonded species, the molar fraction of the latter one increasing with increasing HFP concentration.

It has been recently shown in the case of nitroxides[18] that the variation of the experimental hyperfine splittings is determined mainly by the hydrogen-bonding interaction at low HBD concentration. Thus, by neglecting the macroscopic electrostatic contribution on a_H, we could determine the equilibrium constants K_1 (see eq 1) for the formation of the hydrogen-bonded complex quantitatively from the EPR data by using eq 2.

$$A\bullet + HFP \overset{K_1}{\rightleftharpoons} A\bullet\cdots\cdots HFP \qquad (1)$$
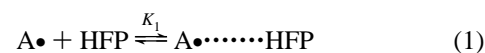
$$a_H = a_{free}X_{free} + a_{bound}X_{bound} \qquad (2)$$

Here a_{free} and a_{bound} represent the values of the hyperfine splitting for the free and hydrogen-bonded radical species,

(17) The increase of the hfs constants at the nuclei of the *para* substituent observed in HFP can be explained on the basis of the polar mesomeric structure H involving spin delocalization on the substituent.
(18) Franchi, P.; Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *ChemPhysChem* **2002**, *3*, 789−793.
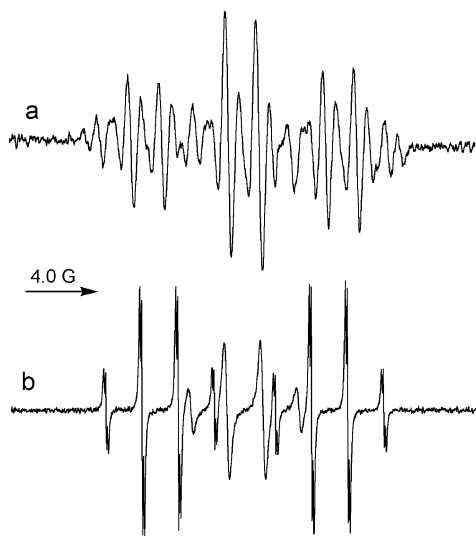
Figure 2. EPR spectra of the phenoxyl radical from **2a** recorded at 293 K in toluene (a) and in a mixture toluene/HFP (70:30) (b). In the lower spectrum, selective line broadening effects are observed.

Figure 3. Plots of log(k) versus $1/T$ for the rotation of the *p*-methoxy group in the radical from **2a**. Rate constants in toluene (■) and in a HFP−toluene mixture 30:70 v/v (●) are reported.

respectively, and X is the corresponding molar fraction. Figure 1, reporting as a solid line the dependence of a_H on the HFP concentration calculated by using eq 2, shows that the experimental data for **2a** and **5a** can be fitted very accurately at low concentration of the fluorinated alcohol. The values of the equilibrium constants for hydrogen-bonding formation, K_1, obtained from these fittings are reported in Table 1 together with the corresponding $\Delta G°$ variation calculated at 293 K. By assuming an entropy change for the formation of hydrogen bonding[18,19] of ca. 11.0 cal mol^{-1} K^{-1}, we could estimate the corresponding enthalpy change as 5.0, 5.4, 5.7, and 5.6 kcal/mol for the phenoxyl radicals derived from **1a**, **2a**, **3a**, and **5a**, respectively.[20]

Thermochemical data for the complexation by HFP of the phenoxyl radical from **4a** have not been determined because of its low solubility in benzene.

HB-Effects on the Rotational Barrier of the *p*-Methoxyphenoxyl Radical. The formation of a hydrogen bond between HFP and a phenoxyl radical leads to an increase of the relative weight of the polar mesomeric structures (E−H), three of which contain a formal double bond between the *para* carbon and the substituent. It is therefore conceivable that complexation of phenoxyl radicals by HBD solvents should induce a larger conformational rigidity about this bond, providing additional evidence for the formation of intermolecular hydrogen bonds.

We therefore examined the room-temperature EPR spectrum of the *p*-methoxyphenoxyl radical in the presence of increasing amounts of HFP. Actually, besides the change in the values of the hyperfine splittings described above, a selective line width broadening not visible in the absence of the fluorinated alcohol started to be observed (see Figure 2). Such a line width effect is indicative of restricted rotation about the Ar−OMe bond that modulates the *ortho*-proton hyperfine splittings. The absolute
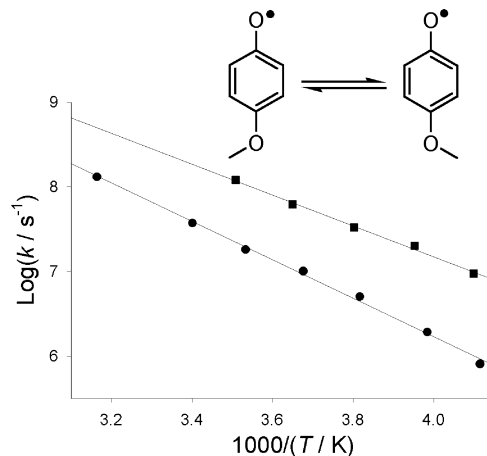
rate constant for the rotation about this bond was determined by simulating the exchange-broadened EPR spectrum recorded in toluene in the presence (a(H) ≈ 0 G, a(H) = 0.23 G, a(3H) = 2.29 G, a(H) = 3.87 G, a(H) = 5.33 G; T = 232 K) and in the absence (a(2H) = 0.46 G, a(3H) = 1.93 G, a(H) = 4.56, a(H) = 6.02 G; T = 218 K) of 30% (v/v) HFP using well-established procedures[21] based on the density matrix theory.[22]

By repeating these measurements at different temperatures (see Figure 3), we obtained the activation parameters for the internal rotation of the methoxy group about the C−O bond as E_a = 8.32 ± 0.40 kcal/mol and log A = 14.5 ± 0.5 in toluene solution and E_a = 10.37 ± 0.45 kcal/mol and log A = 15.2 ± 0.5 in the mixture containing 30% HFP. Thus, the activation energy undergoes an increase of about 2 kcal/mol in the presence of the fluorinated alcohol.

This behavior can be explained as follows: when the O−Me bond of the methoxy group lies on the same plane of the benzene ring, maximum overlap between the lone pair on oxygen and the π-aromatic electrons occurs with a strong conjugative stabilization of the ground state of the phenoxyl radical. On the other hand, when the methoxy group is rotated by 90°, its electron-donating effect is reduced, leading to a weakening of the hydrogen bond interaction. Although solvent effects on the rotational barriers of diamagnetic molecules such as amides[23] have been previously reported, to the best of our knowledge, this is the first example of solvent effects on the rotational energy barrier in an organic free radical.

It is also remarkable that no line broadening effects have been detected in the phenoxyl radical from 2,6-di-*tert*-butyl-4-methoxyphenol (BHA) down to −70 °C in toluene (see Supporting Information). This provides additional evidence that phenoxyl radicals sterically crowded in the proximity of the OH group are not capable of being complexed by HFP through an intermolecular hydrogen bond.

Solvent Effects on the O−H BDE Values. The EPR radical equilibration technique has been very successfully applied by

(19) (a) de Heer, M. I.; Korth, H. G.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 6969−6975. (b) Khafizov, F. T.; Breus, V. A.; Solomonov, B. N.; Kiselev, O. E.; Konovalov, A. I. *Dokl. Akud. Nauk SSRS* **1988**, *303*, 916−919.

(20) The reported strengths (ΔH, kcal/mol) of the hydrogen bonds between HFP and some acceptors follow: 5.9 for acetone, 6.3 for tetrahydrofuran, 5.9 for acetonitrile, and 8.4 for pyridine.[15] The strength for the H-bond between HFP and the radical 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) is instead 5.45.[18]

(21) Guerra, M.; Pedulli, G. F.; Tiecco, M.; Martelli, G. *J. Chem. Soc., Perkin Trans. 2* **1974**, 562−567.

(22) (a) Freed, J. H.; Fraenkel, G. K. *J. Chem. Phys.* **1963**, *39*, 326−348. (b) Hudson, A.; Luckhurst, G. R. *Chem. Rev.* **1969**, *69*, 191−225.

(23) (a) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517−51. (b) Wiberg, K B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261−4270.

us to measure BDE (bond dissociation enthalpies) values of the O–H bond in substituted phenols and of the N–H bond in aromatic amines.[24] This method involves the simultaneous generation of two radicals (eq 3) by continuous UV irradiation, within the cavity of an EPR spectrometer, of di-*tert*-butyl peroxide/benzene solutions of two substrates, AH and BH, present at known concentrations.

$$AH + BH \xrightarrow[\text{Me}_3\text{COOCMe}_3]{h\nu} A\bullet + B\bullet \qquad (3)$$
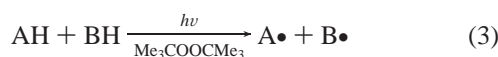
The resulting EPR spectra provide the concentration ratio of the two substrate-derived radicals [A•]/[B•], which is solely determined by the equilibrium of eq 4, if the H-atom transfer between radicals and substrates is sufficiently fast. Thus, by knowing the initial concentrations of the two phenols and the molar ratio [A•]/[B•], determined by integration or by theoretical simulation of the EPR spectrum, we could obtain the equilibrium constant K_4 and the ΔBDE for the couple AH and BH.

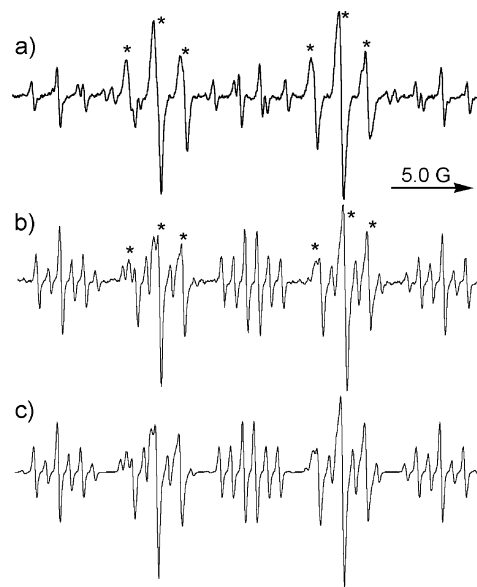$$AH + B\bullet \overset{K_4}{\rightleftharpoons} A\bullet + BH \qquad (4)$$

$$\Delta G^{\circ} = -RT \ln(K_4) \qquad (5)$$

The accuracy of the EPR method relies on the fact that even relatively large errors in the measurement of radical concentrations and therefore of the equilibrium constant, K_4, give rise to small errors in the ΔBDEs because of the logarithmic relation connecting these two quantities (eq 5).

The dependence of the BDE value of a given phenol on the nature of the solvent can, in principle, be investigated with the EPR radical equilibration technique, provided an appropriate reference compound (BH) experiencing a negligible interaction with the solvent is available. In this case, any interaction of the investigated phenol/phenoxyl couple (AH/A•) with the solvent should determine a change in the equilibrium constant easily detectable in the corresponding EPR spectra.

Because we were interested in studying the properties of phenoxyl radicals complexed with hydrogen bond donors (HBDs), an appropriate reference compound not interacting with HBD solvents was required. The most suitable candidates were represented by 2,6-di-*tert*-butyl substituted phenols because the steric protection around the oxygen atom by the bulky *tert*-butyl groups was expected to minimize the formation of hydrogen bonds with HBDs in the phenoxyl radicals.[25] Experimental evidence, based on the solvent dependence of the hfs constants and of the rotational barriers of *para* methoxy groups, that has been reported in the previous sections shows that this is actually the case.

The first step of our investigation was focused on the influence of HFP on the equilibrium of eq 4, where AH is an

(24) (a) Lucarini, M.; Pedulli, G. F.; Cipollone, M. *J. Org. Chem.* **1994**, *59*, 5063–5070. (b) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Fattuoni, C. *J. Org. Chem.* **1996**, *61*, 9259–9263. (c) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Valgimigli, L.; Gigmes, D.; Tordo, P. *J. Am. Chem. Soc.* **1999**, *121*, 11546–11553. (d) Brigati, G.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 4828–4832.

(25) The effect of *tert*-butyl alcohol[26] and ethyl acetate[27] on the equilibrium between a 2,6-di-*tert*-butyl substituted phenol and an unhindered phenol has been previously investigated. On changing the solvent from benzene to HBA solvent, the BDEs were found to increase by ca. 2 kcal/mol for phenols without *ortho* substituents, while in 2,6-di-*tert*-butyl substituted phenols they seem to be substantially unaffected. This behavior has been interpreted by admitting that the BDE increase observed in HBA solvents is essentially due to the solvation of the hydroxylic hydrogen which stabilizes the phenol, leaving the energy of the phenoxyl radical unaltered.

Figure 4. Central part of the room-temperature (293 K) EPR spectra observed under continuous irradiation of a benzene solution of di-*tert*-butyl peroxide (0.2 M), BHT (0.15 M), and **1a** (1.57 M) in the absence (a) and in the presence (b) of 30% HFP. The six inner lines of the EPR spectrum of the radical from BHT are marked with an asterisk. Spectrum c is the theoretical simulation of (b).
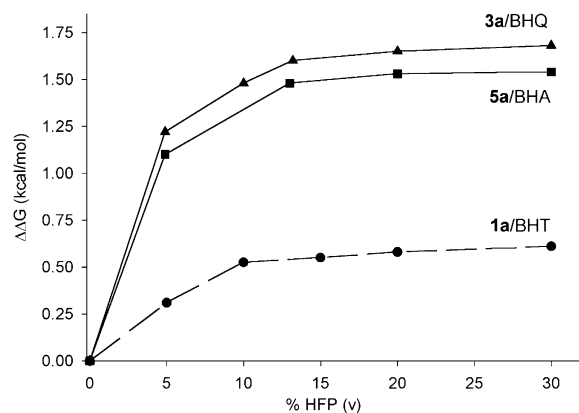
Scheme 3
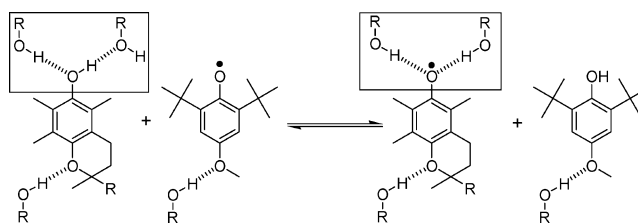
unhindered phenol (**1a–5a**, see Scheme 1) and BH is a 2,6-di-*tert*-butyl substituted phenol (BHT, BHA, and BHQ). We first examined the equilibria involving phenols with the same substituent at the *para* position, that is, the couples trimethyl-phenol (**1a**)/BHT, 2,5-di-*tert*-butylhydroquinone (**3a**)/BHQ, and α-tocopherol (**5a**)/BHA in the presence of variable amounts of HFP. These couples of phenols were chosen to rule out any interaction between the fluorinated alcohol and the ring *para* substituent so that any change in the equilibrium constant is due only to the interaction between HFP and the phenol/phenoxyl oxygen in the unhindered species (see Scheme 3 for the equilibrium between α-tocopherol (**5a**) and BHA).

Figure 4 reports the central part of EPR spectra obtained equilibrating **1a** (1.57 M) with BHT (0.15 M) in benzene and in the presence of 30% HFP. These spectra indicate that when adding HFP the ratio between the two phenoxyl radicals changes, with the trimethylphenoxyl radical becoming the predominant species. Figure 5 shows that, in all three cases, by increasing the alcohol concentration the equilibrium gradually becomes less endothermic until reaching a constant ΔG° value at a concentration of ca. 15% (v/v) HFP.

Table 2 reports the equilibrium constants and the ΔG° values for reaction 4 when HFP is present at 30%. The decrease of endothermicity when the alcohol concentration is increased is an indication that the equilibrium is shifted toward the unhindered phenoxyl radical. Because, as discussed previously, no

Figure 5. $\Delta\Delta G°$ variations for equilibrium 4 as a function of HFP content.

Table 2. Room-Temperature (293 K) Equilibrium Constants and Free Energy Changes of Reaction 4

AH	BH	solvent	K_4	$\Delta G_4°/$ kcal mol^{-1}	$\Delta\Delta G_4°/$[a] kcal mol^{-1}
1a	BHT	Bz[b]	0.0578 ± 0.006	1.66	0.60
		Bz + 30% HFP	0.165 ± 0.018	1.06	
2a	BHT	Bz	0.0462 ± 0.004	1.79	0.87
		Bz + 30% HFP	0.206 ± 0.017	0.92	
3a	BHQ	Bz	0.0228 ± 0.003	2.20	1.68
		Bz + 30% HFP	0.409 ± 0.046	0.52	
3a	BHT	Bz	1.49 ± 0.13	−0.23	1.03
		Bu[c]	22.8 ± 2.6	−1.82	1.59[e]
		Bz + 30% HFP	8.70 ± 0.74	−1.26	
4a	BHT	BuBz[d]	55.0 ± 4.1	−2.16	0.49
		Bu/Bz + 30% HFP	94.8 ± 9.7	−2.65	
5a	BHA	Bz	1.18 ± 0.10	−0.10	1.54
		Bz + 30% HFP	16.72 ± 1.8	−1.64	
BHA	BHT	Bz	105.3 ± 8.9	−2.71	−1.19
		Bu	74.5 ± 8.3	−2.51	−0.20[e]
		Bz + 30% HFP	13.61 ± 1.2	−1.52	
BHQ	BHT	Bz		−2.41	0.70[e]
		Bu		−3.11	

[a] $\Delta\Delta G_4° = \Delta G_{Bz}° - \Delta G_{HFP\ 30\%}°$. [b] Bz = benzene. [c] Bu = *tert*-butyl alcohol. [d] Bu/Bz = *tert*-butyl alcohol/benzene 60/40 (v/v). [e] $\Delta\Delta G_4° = \Delta G_{Bz}° - \Delta G_{Bu}°$.

interaction between HFP and the oxygen atom in the 2,6-di-*tert*-substituted phenols should occur, the large solvent effect on K_4, that is, a 3-, 18-, and 14-fold increase for the couples **1a**/BHT, **3a**/BHQ, and **5a**/BHA, respectively, can be explained by assuming that the interaction with HFP is stronger in the unhindered phenoxyl radical rather than in the corresponding phenol and that the difference in the free energy of solvation is equal to the $\Delta\Delta G°$ values measured by the EPR experiments. A comparison of the three measured $\Delta\Delta G°$ values indicates that the differences in the ability of the phenol and the corresponding phenoxyl radical to accept a hydrogen bond from HFP increase by increasing the electron-donating nature of the *para* ring substituent (Me, OMe, OH). This behavior can be related to the increased electron density at the phenoxyl oxygen when the *para* substituent is an OH or an OMe group.

To study possible solvent effects on the *para*-substituent, we have also investigated the effects of either HFP or *tert*-butyl alcohol on the equilibrium between BHT and BHA (see Scheme 4). Because, in this case, no interaction between the alcohols and the phenolic oxygen is expected due to the presence of the *ortho* bulky substituents, the only appreciable effect should be

Scheme 4
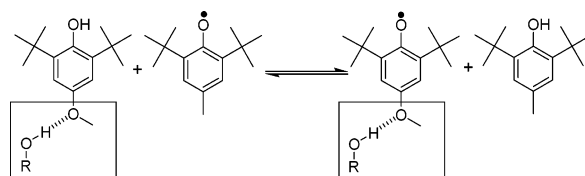
Scheme 5
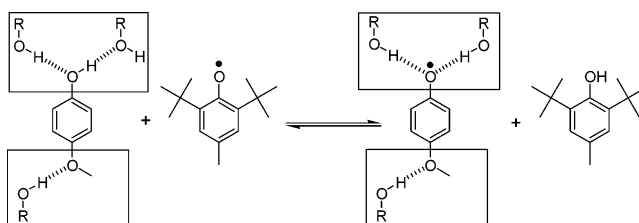
that arising from the interaction between the alcoholic OH and the lone pairs on the ethereal oxygen of BHA. The experimental data indicate (see Table 2) that in the presence of 30% HFP the equilibrium is shifted toward the BHT phenoxyl radical by 1.19 kcal/mol. With a weaker hydrogen bond donor such as *tert*-butyl alcohol, the equilibrium is shifted toward the BHT phenoxyl radical by only 0.20 kcal/mol. The $\Delta\Delta G°$ values indicate that hydrogen bond formation between alcohols and the ethereal oxygen stabilizes BHA more than the corresponding phenoxyl radical, leading to a strengthening of the associated OH bond. The reason is that, on passing from phenol to phenoxyl radical, the hydroxyl group changes its effect from donor to acceptor when becoming a radical oxygen center. Thus, the lone pair electrons of the conjugated OMe group are much less available to accept hydrogen bonding in the phenoxyl radical than in the phenol. It is worth pointing out that these results are consistent with the larger solvent effect found with BHA with respect to BHT when studying the hydrogen transfer reaction between phenols and DPPH in *tert*-butyl alcohol.[9a]

When **2a** and BHT are equilibrated in the presence of 30% HFP, a smaller than expected $\Delta\Delta G°$ value (0.87 kcal/mol) was found. This can be interpreted as the result of two opposite effects (see Scheme 5): one being the preferential complexation by the fluorinated alcohol of the radical oxygen in the phenoxyl radical from **2a** with respect to that of the hydroxyl oxygen of **2a**, and the other is the preferential complexation of the ethereal oxygen in **2a** over that in the corresponding radical. The former interaction induces a decrease of the O−H BDE value, while the latter one has the opposite effect. The positive $\Delta\Delta G°$ is, however, indicative that the dominant effect is the formation of a stronger hydrogen bond with the oxygen of the phenoxyl radical from **2a**.

Equilibration studies have also been done on the couple *p*-aminophenol/BHT. In this case, a quantitative comparison with the previous experiments cannot be made because the equilibrium was investigated in the presence of a large amount of a HBA solvent such as *tert*-butyl alcohol due to the very low solubility of **4a** in benzene. However, also in this case, in the presence of 30% HFP the equilibrium is shifted toward the *p*-aminophenoxyl radical by 0.49 kcal/mol.

To obtain from the equilibrium constants the BDEs of the phenols in the presence of HFP, the entropy change $\Delta S°$ for the hydrogen transfer reaction 4 should be negligible. Because the validity of this assumption is not warranted, especially when

**Table 3.** Bond Dissociation Enthalpies (kcal/mol) in Different Solvents

phenol	benzene[a]	*tert*-butanol	Bz/HFP 30%
1a	82.7[b]	83.6[d]	82.1
2a	82.8	85.0[d]	81.8
3a	80.8	79.2	79.8
4a		78.3	
5a	78.2	79.3[d]	77.8
BHT	81.0	81.0[e]	81.0[e]
BHQ	78.6[c]		79.3
BHA	78.3	78.5	79.5

[a] From ref 24b. [b] Uncertainty in the BDE values is ±0.15 kcal/mol. [c] This work. [d] From ref 26. [e] Assumed.

the equilibrating couple forms and destroys hydrogen bonds in different molecular environments during hydrogen transfer, we studied the temperature dependence of the equilibrium constant K_4 in the case of the couple **1a**/BHT in the temperature range 259−353 K in HFP/toluene 30/70 (v/v) (see Supporting Information). The temperature dependence of the equilibrium constants shows that K_4 changes only slightly with temperature ($\Delta H^\circ = -1.28 \pm 0.25$ kcal mol^{-1} and $\Delta S^\circ = -0.66 \pm 0.64$ cal mol^{-1} K^{-1}), thus indicating that the entropic contribution is so small that it can be safely neglected. If the entropic term is neglected, the OH bond dissociation enthalpy in the presence of HFP can be calculated by using the ΔG° values reported in Table 2. These values are collected in Table 3 together with the values determined by EPR equilibration in *tert*-butyl alcohol (for the discussion of these data, see Computational Details section).

HB-Effects on the Reactivity of Phenoxyl Radicals and of the Parent Phenols. Complexation by HFP of phenoxyl radicals has important effects also on their persistency. Actually, the intensity of EPR spectra is generally higher in the presence of the fluorinated alcohol, this effect being particularly evident in the case of the radical derived from α-tocopherol. In the latter case, the EPR signal persists at room temperature for several hours, demonstrating the enhanced lifetime of the hydrogen-bonded α-tocoperoxyl radical (see Supporting Information). Because the decay of α-tocoperoxyl radicals takes place by a bimolecular disproportionation reaction, to occur in the presence of HFP it requires the desolvation of at least one radical molecule with a consequent reduced reactivity. This behavior is similar to that found for the α-tocoperoxyl radical in the presence of magnesium ions by Nakanishi et al.[28]

To verify if hydrogen bonding on phenoxyl radicals affects also the transfer of a hydrogen atom from phenols, we decided to measure the reactivity of a substituted phenol toward primary alkyl radicals in the presence of HFP at 298 K by the radical clock method. This is based on competition kinetics between a known monomolecular process used as reference and the bimolecular reaction to be timed.[29] The competing monomolecular processes employed were the well-known 5-hexo-cyclization of the 1-hexenyl radical ($k_r = 2.3 \times 10^5$ M^{-1} s^{-1})[30] which has been previously demonstrated to be independent of the nature of the solvent.[11,31] The alkyl radicals were generated

Scheme 6
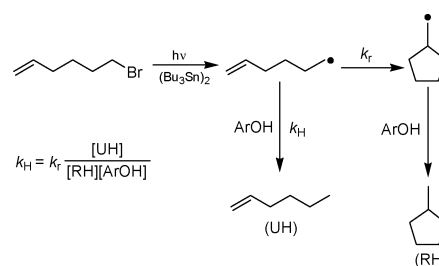
Table 4. Absolute Rate Constants (298 K) for the Abstraction of the Phenolic Hydrogen Atom by Primary Alkyl Radicals Measured in Different Solvents

phenol	solvent	$10^{-5} k_H$ (M^{-1} s^{-1})
α-tocopherol (**5a**)	benzene	6.0 ± 1.5
	tert-butanol	0.32 ± 0.04
	ethyl acetate	0.20 ± 0.03
	HFP/benzene (1/9 v/v)	5.9 ± 1.2
p-methoxyphenol (**2a**)	benzene	2.3 ± 0.42
	tert-butanol (4.8 M)	0.07 ± 0.008
	HFP/benzene (1/9 v/v)	2.0 ± 0.48

by photolyzing oxygen-free solutions of the corresponding bromide in the presence of hexabutyldistannane that was left to react with the phenols (see Scheme 6).[11]

Experimental conditions were chosen to avoid significant consumption of the phenols during the reaction. The reaction products were analyzed by means of GC, and the rate constants for hydrogen abstraction, k_H, obtained by using the equation in Scheme 6 are reported in Table 4.[32] Kinetic experiments were performed with α-tocopherol and *p*-methoxy phenol in benzene, *tert*-butyl alcohol (HBA/HBD solvent), and HFP. As expected, the rate constant for hydrogen abstraction decreased strongly in the presence of the HBA *tert*-butyl alcohol[11] due to the formation of a hydrogen bond between solvent and the hydroxyl proton with a consequent preferential stabilization of the starting phenol with respect to the phenoxyl radical.[33]

This reduced reactivity toward alkyl radicals is consistent with the observed increase of the O−H BDE for **2a** and **5a** in *tert*-butyl alcohol (see Table 3).[25−27] On the other hand, in the presence of a strong hydrogen bond donor such as HFP the reactivity is almost coincident to that in benzene, this being in disagreement with the equilibration experiments that indicated a reduced strength of the phenolic OH bond. To better understand the reason for this surprising discrepancy between the thermodynamic and kinetic experiments, we performed some DFT calculations.

DFT Results. The effect of HFP on the thermodynamic and kinetic properties has been investigated by comparing the DFT results for the phenol/phenoxyl−(HFP)$_n$ supermolecule complexes with those obtained while employing in the calculations a good HBA solvent (2-propanol) and an apolar solvent (propane).

(26) Pedrielli, P.; Pedulli, G. F. *Gazzetta* **1997**, *127*, 509−512.
(27) Unpublished results.
(28) Nakanishi, I.; Fukuhara, K.; Shimada, T.; Ohkubo, K.; Iizuka, Y.; Inami, K.; Mochizuki, M.; Urano, S.; Itoh, S.; Miyata, N.; Fukuzumi, S. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1520−1524.
(29) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317−323.
(30) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739−7742.

(31) (a) Maeda, Y.; Schmid, P.; Griller, D.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1978**, 525−526. (b) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983−4992.
(32) Under our conditions, products deriving from the reactions between phenoxyl and alkyl radical to give radical−radical recombination products were not observed.
(33) The first report providing clear quantitative evidence of the role that hydrogen bonding plays on the H-atom donor activities of phenols has been reported by Ingold and co-workers: Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Green, W. H.; Procopio, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 2929−2930.

Scheme 7
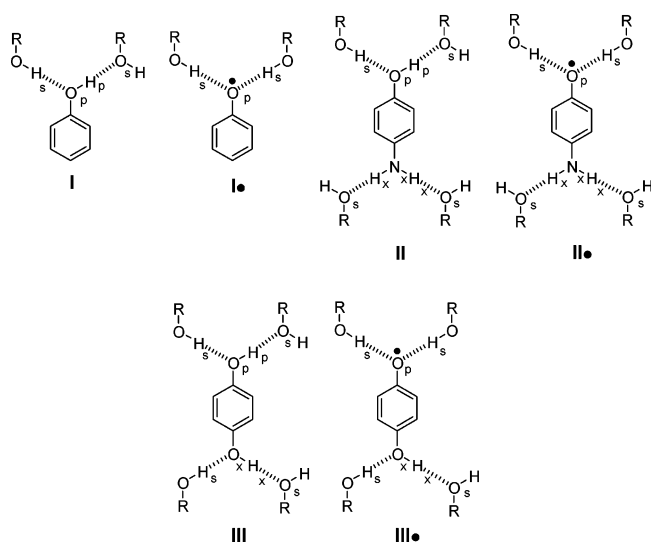
Chipman[10c] using DFT calculations showed that water hydrogen-bonding effects on the structure, vibrational frequencies, and hfs constants of phenoxyl and *p*-aminophenoxyl radicals are well accounted for by considering the interaction of the radical species with two and four hydrogen-bonded water molecules, respectively, that is, two water molecules for each substituent. An analogous approach has been used in the present study. First, we examined the interaction of two solvent molecules with the unsubstituted phenol (PhOH) and with the corresponding phenoxyl radical (PhO•) by placing one molecule of solvent near the O-atom (HBD interaction: the solvent behaves as hydrogen bond donor) and one near the hydroxyl H-atom (HBA interaction: the solvent behaves as hydrogen bond acceptor) of PhOH (structure **I** in Scheme 7) and two molecules of solvent interacting with the O-atom (two HBD interactions) in PhO• (structure **I•**).

We then examined the interaction of the solvent with *para*-substituted phenols *p*-X-PhOH (X = NH₂, OH, OMe) and with the corresponding radical species placing two additional molecules of solvent near the *para*-X group. Two HBA interactions were considered with the amine group (structures **II** and **II•**), and one HBA plus one HBD interaction with the methoxy and hydroxyl group (structures **III** and **III•**). In the discussion, the strength of these interactions was qualitatively related to the atomic distance of the interacting atoms.

The O−H BDE values for phenols (ArOH) have been computed using the isodesmic reaction

$$ArOH + PhO• \rightleftharpoons ArO• + PhOH \qquad (6)$$
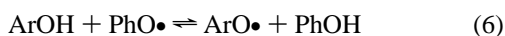
in conjunction with the experimental O−H BDE value for phenol as

$$BDE(ArOH) = BDE_{exp}(PhOH) + [E_{calc}(ArO•) - E_{calc}(ArOH)] - [E_{calc}(PhO•) - E_{calc}(PhOH)] \quad (7)$$

to cancel out errors due mainly to electron correlation.

Table 5 shows that the BDEs for *para*-substituted phenols computed with the B3LYP-DFT method using the isodesmic approach are in excellent agreement with the experimental values even employing a small double ζ basis set (6-31G*). An estimate of the zero point vibration energy (ZPVE), thermal

Table 5. O−H BDE (kcal mol⁻¹) for *para*-Substituted Phenols Computed with the B3LYP Method

	isodesmic approach				absolute BDE	
	6-31G*	6-31G* + ZPVE	6-31G* (ΔH_{298})	6-311++G** //6-31G*	LDBS[a] (ΔH_{298})	expt[b]
H	88.3	88.3	88.3	88.3	87.1	88.3
Me	86.5	86.6	86.5	86.3	84.6	86.2
OMe	82.9	83.3	83.2	82.5	80.9	82.8
OH	82.9	83.4	83.3	82.9		
NH₂	79.9	80.2	80.1	79.5	77.7	79.5[d]
MAD[c]	0.27	0.53	0.43	0.13	1.77	

[a] From ref 34. *[b]* From ref 24b. *[c]* Mean absolute deviation. *[d]* Estimated from the substituent additivity rules (ref 24d).

Table 6. BDE Values for PhOH and Activation Energy E_a for Hydrogen Atom Abstraction from PhOH by Methyl Radical Computed with the B3LYP Method in the Presence of Two Molecules of Solvent

	BDE[a] (kcal mol⁻¹)			E_a (kcal mol⁻¹)	
solvent	6-31G*	6-31G* + ZPVE	6-311++G** //6-31G* + ZPVE[b]	6-31G*	6-31G* + ZPVE
propane	87.8 (−0.5)	87.9 (−0.4)	88.2 (−0.1)	3.4	2.2
2-propanol	91.3 (3.0)	91.4 (3.1)	91.7 (3.4)	7.4	6.3
HFP	85.9 (−2.4)	86.1 (−2.2)	85.6 (−2.7)	3.0	2.0

[a] Values relative to gas-phase calculations are reported in parentheses. *[b]* ZPVE computed at the B3LYP/6-31G* level.

correction to the enthalpy, as well as enlargement of the basis set (6-311++G**) have negligible effects.

The mean absolute deviation (MAD) indicates that agreement with experiment is slightly better than that shown by the absolute values computed recently with the B3LYP method[34] in conjunction with the locally dense basis set (LDBS) approach.[35]

Table 6 shows that an apolar solvent such as propane has little effect on the OH BDE value of phenol while a strong HBA solvent such as 2-propanol increases considerably the BDE value in agreement with experiments.[27−29] DFT calculations on the phenol/phenoxyl−(HFP)₂ supermolecule complexes confirm that the fluorinated solvent has an effect opposite to 2-propanol because it decreases the BDE of phenol.

The measure of the atomic distances reported in Table 7 suggests that 2-propanol interacts more efficiently with the starting phenol as hydrogen bond acceptor rather than with the phenoxyl radical as hydrogen bond donor. On the other hand, with HFP, the stabilization of the phenoxyl radical by formation of a strong three-center hydrogen bond overcompensates the interaction with the starting phenol as suggested by the ESR experiment. Interestingly, the variation of the O−H BDE produced by different solvents computed at the B3LYP/6-31G* level is similar to that computed with the large 6-311++G** basis set and estimating the ZPVE correction at the 6-31G* level. Hence, the effect of solvents on the BDEs can be studied explicitly using the isodesmic approach even when phenols and phenoxyl radicals interact with four molecules of solvent as in *para*-substituted phenols.

The effect of propane on the O−H BDE of *para*-substituted phenols was not studied because this apolar solvent has little effect on the BDE of phenol. First, the effect of 2-propanol on the O−H BDE of *para*-substituted phenols *p*-X-PhOH has been

(34) Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173−1183.
(35) DiLabio, G. A. *J. Phys. Chem. A* **1999**, *103*, 11414−11424.

Table 7. Relevant Atomic Distances^a d (Å) for the Interaction of Two Molecules of Solvent with PhOH, PhO• (in Parentheses), and [PhOH−Me•]‡ Computed at the B3LYP/6-31G* Level

solvent	PhOH (PhO•)			[PhOH−Me•]‡			
	$d(O_P{-}H_S)$	$d(H_P{-}O_S)$	$d(O_P{-}H_P)$	$d(O_P{-}H_S)$	$d(H_P{-}O_S)$	$d(O_P{-}H_P)$	$d(H_P{-}C)^b$
propane	2.663 (2.666, 2.708)		0.969	2.687, 2.702		1.114	1.457
2-propanol	1.911 (1.949, 1.965)	1.746	0.989	1.968, 1.998	2.953	1.137	1.429
HFP	1.780 (1.817, 1.858)	1.796	0.979	1.796, 1.968	2.738	1.117	1.453

^{a} P = phenol/phenoxyl; S = solvent (see Scheme 7). ^{b} C = carbon of attacking methyl radical.

Table 8. O−H BDE (kcal mol^{-1}) for *para*-Substituted Phenols Computed in the Presence of n Molecules of Solvent at the B3LYP/6-31G* Level (Values Relative to the Corresponding Gas-Phase BDEs Are Reported in Parentheses)

X	2-propanol			HFP		
	$n = 4$	$n = 2$ near OH/O•	$n = 2$ near X	$n = 4$	$n = 2$ near OH/O•	$n = 2$ near X
H		91.3 (3.0)			85.9 (−2.4)	
Me					83.6 (−2.9)	
OMe	85.3 (2.4)	84.6 (1.7)	83.2 (0.3)	79.8 (−3.1)^a	78.5 (−4.4)	84.7 (1.8)^a
OH	82.6 (−0.3)	84.4 (1.5)	81.7 (−1.2)	78.8 (−4.1)	78.5 (−4.4)	83.6 (0.7)
NH$_2$	73.7 (−6.2)	80.1 (0.2)	75.8 (−4.1)	71.4 (−8.5)	74.0 (−5.9)	78.4 (−1.5)

^{a} Only one molecule of HFP near X (see text).

Table 9. Relevant Atomic Distances^a d (Å) for the HBD and HBA Interactions Involving the X Group in *para*-Substituted Phenols p-X-C$_6$H$_4$OH Interacting with Four Molecules of Solvent at the B3LYP/6-31G* Level (Values for Phenoxyl Radicals Are Reported in Parentheses)

X	2-propanol			HFP		
	$d(O_X{-}H_S)$	$d(H_X{-}O_S)$	$d(C{-}X)$	$d(O_X{-}H_S)$	$d(H_X{-}O_S)$	$d(C{-}X)$
OMe	1.937 (2.017)	2.835 (2.768)	1.376 1.348	1.947 (2.018)	b	1.374 (1.352)
OH	1.900 (2.005)	1.761 (1.690)	1.370 (1.344)			
NH$_2$		2.080, 2.104 (1.914, 1.948)	1.399 (1.350)		2.208, 2.220 (1.967, 2.044)	1.405 (1.353)

^{a} S = solvent (see Scheme 7). ^{b} One molecule of HFP near X.

studied at the simple B3LYP/6-31G* level. Further calculations were carried out by placing only two molecules of 2-propanol either at the OH/O• site or at the X site to study separately the interactions of the solvent with the OH/O• group and the *para* substituent. Table 8 shows that the presence of four molecules of 2-propanol strongly decreases the BDE value for *p*-amino-phenol as suggested by the experimental results (see Tables 3 and 5).

The measure of the atomic distances reported in Table 9 indicates that this lowering is due to the strong increase of the HBA interaction between 2-propanol and the amine group on going from *p*-aminophenol to the *p*-aminophenoxyl radical. In the radical species, this interaction is stronger because of the larger weight of a polar resonance structure having a positive charge on the N-atom and a formal C−N double bond (see Scheme 2). Actually, the C−N bond length decreases considerably in the radical species.

For X = OH, the measure of the atomic distance indicates that 2-propanol interacts with the *para*-OH group both as a strong H-bond acceptor and as a weak H-bond donor. These interactions produce an opposite effect on the BDE. The decrease of BDE on going from the gas phase to the super-molecule complex in which 2-propanol interacts only with the *para*-OH group confirms that the HBA interaction prevails. The

stabilization of the phenoxyl radical produced by this HBA interaction at the substituent counterbalances the stabilization of the phenol produced by the HBA interaction of 2-propanol with the phenolic OH group previously described, so that 2-propanol slightly reduces the O−H BDE. Indeed, a decrease of BDE for **3a** on going from an apolar solvent to alcohols (see Table 3) was found experimentally.

As expected, for X = OMe, the HBA interaction of 2-propanol with the *para*-methoxy group is negligible (see Table 9 and Figure 6), and the BDE value in the presence of such a strong HBA solvent increases similarly to the unsubstituted phenol, the variation being slightly lower. Table 8 shows that the effect of 2-propanol on the BDE due to interactions with the OH/O• and X groups is not additive. The electronic effect of the *para* substituent X on the HBA interaction of 2-propanol with the phenoxylic group should be influenced by the change of π electron density at X produced by interactions of 2-propanol with the X group. This indirect effect should decrease largely the computed BDE for X = NH$_2$ and moderately that for X = OH and increase the BDE for X = OMe in accord with calculations.

The effects of HFP have then been investigated. For X = OMe, only one molecule of HFP was placed near the methoxy group because the HBA interaction of 2-propanol with the methyl of the methoxy group was found to be negligible. Interestingly, in accord with the BHT/BHA radical-equilibrium EPR experiment, the HBD interaction of HFP with the methoxy group stabilizes the starting phenol with respect to the phenoxyl radical because the polar structures in the radical species (E−H of Scheme 2) bring a formal positive charge at the ethereal oxygen. As expected, the increase of BDE is much larger in HFP (1.8 kcal mol^{-1}) than in 2-propanol (0.3 kcal mol^{-1}), in excellent agreement with the BDE determined experimentally for BHA in different solvents (see Table 3). For X = OH, the weak HBA interaction of HFP with the hydrogen of the *para*-OH group produces an opposite effect and reduces the de-stabilization of the radical species in excellent agreement with
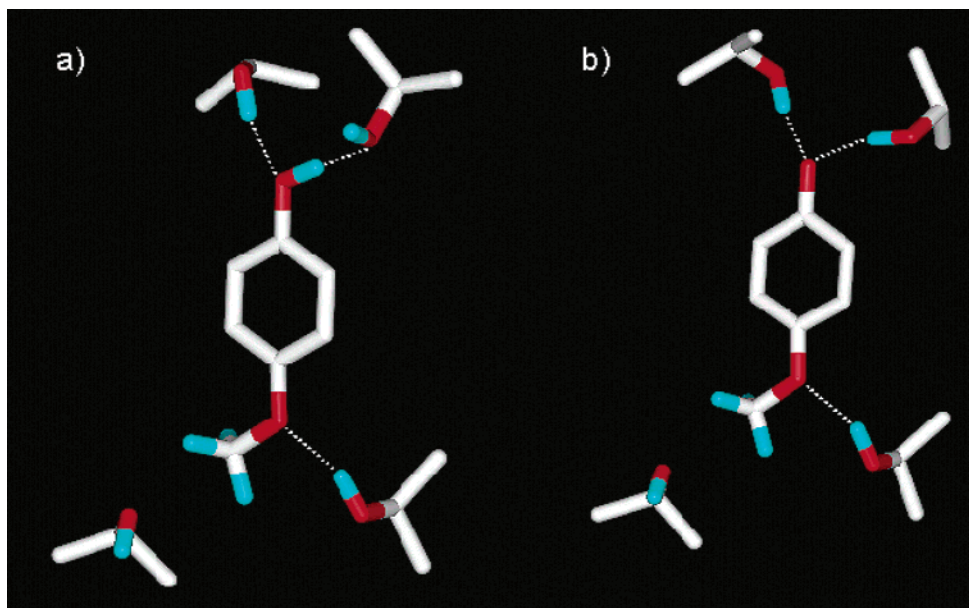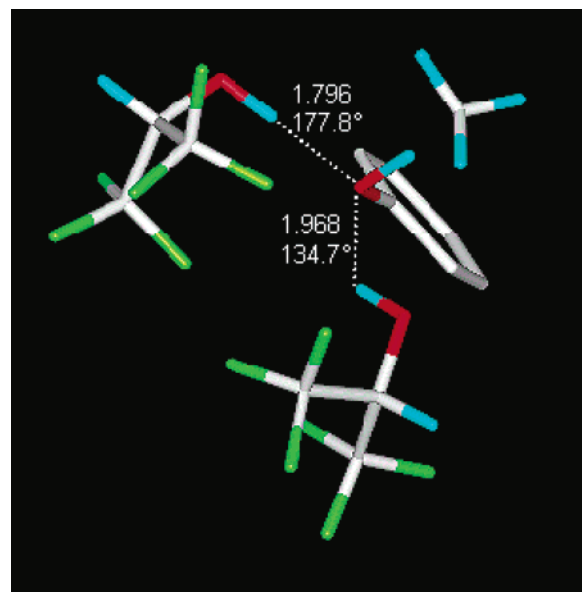
Figure 6. B3LYP/6-31G* calculated structures of *p*-methoxyphenol (a) and *p*-methoxyphenoxyl radical (b) with H-bonded 2-propanol molecules. Aliphatic and aromatic hydrogens have been removed for clarity.

the trend observed experimentally for the BDE value of BHQ with the addition of HFP to benzene.

The solvent effect on the BDE of *p*-aminophenol is significantly stronger in 2-propanol than in HFP, the decrease of O−H BDE with respect to the unsubstituted phenol being 9.2 and 6.1 kcal mol^{-1}, respectively. This is in accord with the weak HBA character of HFP as confirmed by the measure of the atomic distances reported in Table 9.

Calculations were also carried out on the *p*-methoxyphenoxyl radical to determine the effect of HFP both on magnetic (hfs constants) and on energetic (barrier E_{rot} to the internal rotation of the *para*-methoxy group) properties. At the UB3LYP/6-31G* level, the sum of the *ortho* hfs constants decreases in absolute value from −13.39 to −11.84 G in accord with the ESR results displayed in Figure 1. The UB3LYP/6-31G* rotation barrier increases from 6.8 kcal mol^{-1} computed in the gas phase to 8.4 kcal mol^{-1} in HFP in good accord with the variation of the rotational barrier produced by adding HFP to a toluene solution as determined by the line width broadening of the ESR spectra. The ΔE_{rot} (1.6 kcal mol^{-1}) is slightly smaller than that observed experimentally (2.06 kcal mol^{-1}). The computed E_{rot} (8.3 kcal mol^{-1}) does not change significantly in calculations performed placing only two molecules of HFP near the phenoxylic group. Thus, the observed increase of E_{rot} is due to a reduction in the transition state of the strong HBD-stabilizing interaction of HFP with the phenoxylic oxygen produced by the decrease of the electron-donating effect of the *para* substituent that depends on the π conjugation. Interestingly, the O−H BDE increases by 3.5 kcal mol^{-1} (i.e., BDE = 83.3 kcal mol^{-1}) upon rotation of the methoxy group by 90°. This value is close to the BDE for *p*-methylphenol (83.6 kcal mol^{-1}) computed in the same solvent. This finding is in accord with the experimental evidence that *p*-methoxy substituents constrained in the orthogonal conformation by *meta* bulky groups have the same effect of a *para* methyl group on the BDE of phenols.[34]

Finally, we have investigated the effect of solvent on the activation energy E_a for the hydrogen atom abstraction from phenol by methyl radical. Table 6 shows that the effect of the

Figure 7. B3LYP/6-31G* calculated transition state structures for hydrogen abstraction from phenol by methyl radical in the presence of two HFP molecules. Numbers refer to atomic H_S−O_P distances (Å) and $\angle O_P H_S O_S$ bond angles.

nature of the solvent on the activation energy E_a does not follow the same trend as found for the O−H BDEs. The E_a value in the presence of two molecules of 2-propanol is much higher than in the other two cases as expected for a strong HBA solvent that stabilizes to a larger extent the phenol rather than the transition state. On the other hand, a HBD solvent might be expected to decrease considerably E_a with respect to an apolar solvent stabilizing preferentially the transition state. The decrease of E_a is, however, small on going from propane to HFP. Actually, the atomic O_P−H_S distances (1.796 and 1.968 Å) reported in Table 7 and the corresponding $\angle O_P H_S O_S$ bond angles (177.8° and 134.7°) indicate that, in the transition state computed in the presence of HFP, the second HBD interaction is much weaker than that found in phenoxyl radicals (see Figure 7).

Thus, the phenoxyl radical is not yet strongly stabilized by HFP as expected for an early transition state. Actually, the O−H bond (see $d(O_P−H_P)$ values in Table 7) is stretched to a length much shorter than the distance of the transferring hydrogen from the abstracting carbon, $d(H_P−C)$. It is worth noting that these atomic distances are similar in HFP and propane, while the former is longer and the latter is shorter in 2-propanol as expected for a transition state having higher activation energy. As expected, the most evident change in the structural parameters of the phenol in the transition state is the rotation of the O−H bond from the planar to a nearly orthogonal conformation, the out-of-plane dihedral angle being 80.4° in HFP. This is a consequence of the fact that in the hydrogen atom transfer the π conjugated lone pair on oxygen in phenol must transform into an in-plane σ lone pair in the phenoxyl radical.[8a]

Conclusions

The present experimental and computational study demonstrates that hydrogen bond donors can significantly change the spectroscopic and thermochemical properties of phenoxyl radicals. Thus, a strong H-bond donor such as hexafluoropropanol produces large variations of the hyperfine splitting constants indicative of a large redistribution of electron spin density which can be accounted for by the increased importance of the mesomeric structures (E−H) with electric charge separation. The conformational rigidity of phenoxyl radicals with electron-releasing substituents is also greatly enhanced in the presence of HFP, this being due to the fact that three of the polar structures (E−H) contain a formal double bond between the aromatic ring and the substituent.

As far as the effect on the thermochemistry is concerned, it has been found that in phenol and alkyl substituted phenols the O−H bond dissociation enthalpy, which in HBA solvents is larger than in hydrocarbons due to the preferential stabilization of the starting phenol with respect to the phenoxyl radical, is lowered in the presence of HBD solvents because they preferentially stabilize the phenoxyl radical.

In phenols containing groups such as OR that are acceptors of H-bonds, the interaction between the HBD solvent and the substituent is stronger in the phenol than in the corresponding phenoxyl radical because the radical oxygen behaves as an electron-withdrawing group which decreases the complexating ability of the substituent. This interaction partially compensates the stabilizing effect on the phenoxyl radical due to the H-bond formation at the radical oxygen, so that the overall effect of HBD solvents is a decrease of the BDE value smaller that in the case of alkyl substituted phenols.

A similar behavior is also experienced, in the presence of HBD solvents, by phenols containing OH and NH₂ groups. Actually, phenols such as **3a**, **4a**, and BHQ display a previously unreported effect when dissolved in the HBA solvent *tert*-butyl alcohol because, instead of showing an increase of the O−H BDE value as usual, they undergo a weakening of the phenolic bond. The reason is that the stabilizing interaction between solvent and the substituent is much stronger in the phenoxyl radical than in the parent phenol because of the electron-withdrawing effect of the radical oxygen, which makes more acidic, and therefore more available to give H-bonds, the OH or NH groups. This interaction between HBA solvent and substituent in the radicals exceeds the stabilizing interaction of

the solvent with the phenolic OH group, so that the global effect is a decrease of the BDE value.

The effect of HBD solvents on the reactivity is more puzzling. In general, it has been found that the reactivity of phenols is strictly correlated with their BDE values;[24b,36] accordingly, the logarithm of the rate constant for the reactions with peroxyl[37] or alkyl radicals[11] in the presence of HBA solvents decreases parallel to the increase of the strength of the O−H bond, while, in HBD solvents, the decrease of BDE is not accompanied by a larger reactivity. The origin of this unexpected behavior has been shown by DFT calculations, for the reaction with methyl radical, to depend on the early character of the transition state that resembles more the reagents than the products, so that the stabilization of the phenoxyl radical by H-bond complexation does not have any effect on the reactivity of the parent phenol. A remarkable effect of H-bond complexation is instead represented by the much greater persistency of phenoxyl radicals, for example, the α-tocopheroxyl radical, observed in the presence of HFP. More detailed kinetic studies are however required to clarify the reason for this behavior.

Experimental Section

Materials. Solvents were of the highest purity grade commercially available and were used as received. Phenols **1a−4a**, BHT, and BHA were commercially available and were used as received. α-Tocopherol was purified by column chromatography on silica gel according to a previously described method.[11] Hexa-*n*-butylditin and 6-bromo-1-hexene were stored under nitrogen at 5 °C. Di-*tert*-butylperoxide was percolated through activated basic alumina and stored at 5 °C. BHQ was prepared according to literature by reducing the corresponding 2,6-di-*tert*-butyl quinone.[38]

EPR Experiments. Deoxygenated benzene solutions containing the phenol under investigation (0.1−0.5 M), an appropriate reference phenol (0.1−0.5 M), and di-*tert*-butyl peroxide (5% v/v) were sealed under nitrogen in a suprasil quartz EPR tube. The sample was inserted in the thermostated cavity of an EPR spectrometer and photolyzed with the unfiltered light from a 500 W high-pressure mercury lamp. The temperature was controlled with a standard variable temperature accessory and was monitored before and after each run with a copper-constantan thermocouple.

The EPR spectra were recorded on a Bruker ESP 300 spectrometer equipped with a Hewlett-Packard 5350B microwave frequency counter for the determination of the *g*-factors, which were corrected with respect to that of perylene radical cation in concentrated H_2SO_4 ($g = 2.00258$).

The molar ratio of the two equilibrating radicals was obtained from the EPR spectra and used to determine the equilibrium constant, K_4, by introducing the initial concentrations of the two reactants. Initial concentrations were high enough to avoid significant consumption during the course of the experiment. Relative radical concentrations were determined by comparison of the digitized experimental spectra with computer simulated spectra. In these cases, an iterative least-squares fitting procedure based on the systematic application of the Monte Carlo method was performed to obtain the experimental spectral parameters of the two species including their relative intensities.[24b]

Kinetic Measurements. In a typical experiment, 200 mL of a solution of the phenol (0.1−1 M) containing 6-bromo-1-hexene (0.005−0.01 M) and hexa-*n*-butylditin (0.01 M) was sealed in a quartz tube, after being deoxygenated by bubbling nitrogen. The reaction mixtures were then irradiated for 30−120 min at 298 K in a thermostated

(36) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053−7065.
(37) Valgimigli, L.; Banks, J. T.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1999**, *64*, 3381−3383.
(38) Worrel, C. J.; McLean, R. L. U.S. Patent 3415850, 1968.

photoreactor, built in our laboratories, equipped with a 125 W high-pressure mercury lamp, and the products were analyzed by gas chromatography. For each phenol, in each solvent or solvent mixture, four measurements were made with a different phenol concentration, and the reaction products ratio [UH]/[RH] was plotted versus the phenol concentration to obtain the k_H/k_r ratio by linear regression of the experimental data.

Computational Details. DFT calculations with the B3LYP functional[39,40] were carried out on *para*-substituted phenols *p*-X-PhOH (X = H, Me, NH$_2$, OH, OMe) and on the corresponding phenoxyl radicals using the Gaussian 98 system of programs.[41] The unrestricted wave function was used for radical species. Geometries were obtained employing a valence double-ζ basis set supplemented with polarization d-functions on heavy atoms (6-31G*).[42] Single point calculations were performed using a valence triple ζ basis set augmented with diffuse functions[43] (6-311++G**). Zero point vibrational energies (ZPVE) were computed at the B3LYP/6-31G* level from frequency calculations using a scaling factor of 0.9806 to account for anharmonicity.[44] O—H BDEs were computed using the isodesmic approach. Activation energy E_a for hydrogen abstraction from phenol by methyl radical in the presence of two molecules of solvent has been computed at the B3LYP/6-31G* level. The nature of the transition states was verified by frequency calculations (one imaginary frequency), and the ZPVE correction was also estimated.

Supporting Information Available: EPR spectra and experimental plots (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA034963K

(39) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

(40) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(41) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A., Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(42) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213−222.

(43) Clark, T.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294−301.

(44) Scott, P. A.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.