

Reactivity of Substituted Phenols Toward Alkyl Radicals

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Abstract: The rate constants for the reaction of primary alkyl radicals with substituted phenolic compounds have been measured in benzene or toluene at room temperature by using the radical clock technique. With three representative phenols, containing in the *ortho* positions substituents of different size, the kinetics of the hydrogen transfer to alkyl radicals was studied at different temperatures to obtain the corresponding Arrhenius parameters. The kinetic solvent effect on the reaction with α -tocopherol was also investigated in six different solvents behaving as hydrogen bond acceptors, while the reaction with 2,4,6-trimethylphenol and 2,6-di-*tert*-butylphenol was studied in toluene and γ -valerolactone. For some phenols, the effect of self-aggregation on the kinetic parameters was also studied.

Antioxidants are used as additives in food, lubricants, polymers, paints, etc. to retard the spontaneous or photoinduced oxidation of these materials. They are also widespread in nature where they fulfill the task of protecting lipids from oxidative degradation.¹ Phenols and aromatic amines are radical-trapping antioxidants which readily transfer the hydrogen atom bound to the heteroatom to the peroxy radicals which carry the oxidation reaction's radical chain.

Hydrogen atom transfer from a phenolic antioxidant yields a hydroperoxide and a resonance-stabilized (and often persistent) aryloxy radical (eq 1) that captures a second peroxy radical, thus affording nonradical products (eq 2).²



There is a voluminous literature concerning the determination of the absolute rate constants for hydrogen atom abstraction from phenols by peroxy radicals^{2–7} and by other oxygen- or nitrogen-centered radicals.⁸ Many of these rate constants have been measured in different media and found to show dramatic

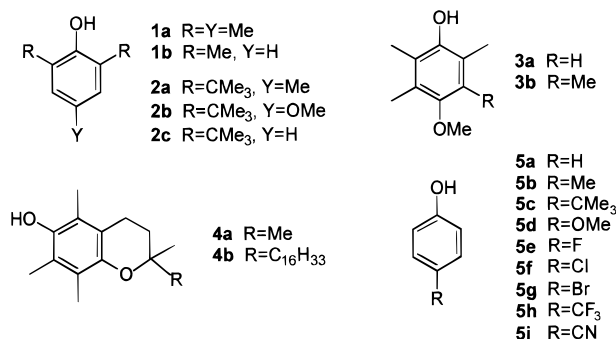
solvent effects in hydrogen bond accepting solvents (HBA).^{9–11} The magnitudes of these solvent effects are essentially identical for the same phenol, that is, they do not depend on the nature of the attacking radical. These solvent effects have been attributed to hydrogen bond formation between the phenol's hydroxylic hydrogen atom and the HBA solvent.

On the other hand, very little is known about the absolute rate constants for hydrogen atom abstraction from phenols by carbon-centered radicals. Ingold and co-workers¹² carried out radical clock^{13,14} competitive kinetic experiments by reacting α -tocopherol with 5-hexenyl radicals for which hydrogen atom abstraction competes with their cyclization to cyclopentylmethyl radicals. The rate constant for hydrogen atom abstraction was calculated to be $1.7 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 70 °C in benzene. Ruegge and Fischer¹⁵ used a kinetic EPR method to measure the rate constants for the reactions of HOCH_2^\bullet and *tert*-butyl radicals with 2,6-di-*tert*-butylphenol in heptane at room temperature and obtained values of 702 and 93 $\text{M}^{-1} \text{ s}^{-1}$, respectively.

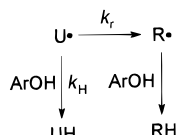
In the present paper we report the results of a kinetic investigation on the hydrogen atom transfer from several substituted phenols to primary alkyl radicals. We chose this reaction since hydrogen abstraction from phenols by carbon-centered radicals is relevant to the inhibition of radical polymerization and to the inhibited autoxidation of organic materials

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Chart 1



Scheme 1



at low oxygen partial pressure.^{16–19} We also wanted to check whether the principle that kinetic solvent effects on hydrogen atom abstractions from phenols are independent of the nature of attacking radical could be extended from heteroatom-centered to carbon-centered radicals. Finally, since Ingold and co-workers²⁰ have proposed that kinetic solvent effects measurements can be used to obtain equilibrium constants for hydrogen bonding of phenols to hydrogen bond acceptors, we have checked the validity of this proposal by comparing the values obtained from kinetic data with those determined by FT-IR measurements.

Results

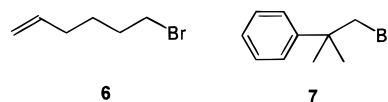
Rate constants for the reaction of phenols **1a–b**, **2a–c**, **3a–b**, **4a–b**, and **5a–i** with primary alkyl radicals were determined by using the radical-clock method,^{13,14} which is based on the use of an unrearranged radical U• that can undergo intramolecular reaction to afford a rearranged radical R• in competition with hydrogen atom abstraction from a phenol (Scheme 1).

If the absolute rate constant for rearrangement, k_r , is known and the concentration of ArOH is approximately constant during the reaction, the measure of the relative yields of the unrearranged, UH, and rearranged, RH, hydrocarbons provides the rate constant for hydrogen abstraction, k_H (eq 3).^{13,14}

$$k_H = k_r \frac{[\text{UH}]}{[\text{RH}][\text{ArOH}]} \quad (3)$$

Radical clocks suitable for these measurements must rearrange at a rate comparable to that of hydrogen atom abstraction from the chosen phenol. The rearrangement of the 5-hexenyl radical²¹ to the cyclopentylmethyl radical was found to be suitable for phenols **1a**, **3a–b**, **4a–b**, and **5d** but it was too fast to compete with the hydrogen abstraction from phenols **1b**, **2a–c**, **5a–c**,

and **5e–i**. For these last phenols the neophyl radical was chosen because it undergoes a much slower rearrangement.^{22, 23}



The rate constant for the reaction of α -tocopherol (α -TOH) with the 5-hexenyl radical has been previously measured by Ingold and co-workers by thermolyzing diheptenoyl peroxide at 70 °C for 5 days in a benzene solution containing α -TOH.¹² We preferred to generate the primary alkyl radical photochemically (eqs 4 and 5) from the corresponding bromoalkanes, **6** and **7**, and hexa-*n*-butylditin, since this allowed us to carry out the reactions over a wide range of temperatures. In our experiments, the concentration of bromides **6** and **7** was always ca. 20 times lower than that of the phenol (0.1–1.5 M), so that the amount of ArOH consumed during the reaction could be neglected.



The reaction of 2,6-di-*tert*-butyl-4-methoxyphenol (**2b**) with neophyl radicals gave considerable amounts of β,β -dimethylstyrene. This olefin is formed by reaction of the rearranged PhCH₂CMe₂• radical with the phenoxy radical from **2b** (eq 6), the latter is very persistent and accumulates in solution, eventually reaching a relatively high concentration.²⁴ Thus, under our conditions, the radical–radical reaction 6 becomes competitive with the much slower hydrogen abstraction by PhCH₂CMe₂• from phenol **2b**. To allow for the fact that the rearranged radical from neophyl reacts to give both isobutylbenzene, PhCH₂CHMe₂, and β,β -dimethylstyrene, the sum of the concentrations of these two products was introduced in the denominator of eq 3 when calculating k_H for **2b**.



Ortho-Substituted Phenols. The 5-hexenyl clock was used with the more reactive phenols. These reactions were carried out in toluene, which did not interfere with the reactions of interest. The rate constants for rearrangement of this radical clock at room temperature (298 K) is $2.3 \times 10^5 \text{ s}^{-1}$, and its dependence on temperature is given by the following expression: $\log(k_r/\text{s}^{-1}) = 10.4 - 6.85/(2.3RT)$.²¹

The experimental data obtained at room temperature in toluene for phenols **1a**, **3a**, **3b**, and **4a** are shown in Figure 1. In all cases the intercepts of the regression lines on the vertical axis (reporting the [UH]/[RH] ratio) are close to zero. This means that only the rearranged hydrocarbon is formed at very low phenol concentrations, i.e., no other species in solution, including the toluene solvent, competes with these phenols as hydrogen atom donor to the 5-hexenyl radical. On the other hand, with the less reactive phenols **1b** and **2a–c** (for the sake of comparison with the previous radical clock, measures were also repeated for **1a**), for which the slower neophyl radical clock (Figure 2a) was used ($k_r^{298} = 1.1 \times 10^3 \text{ s}^{-1}$, $\log(k_r/\text{s}^{-1}) = 10.98$

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

(18) Lilles, H.; Parnel, R. D.; Russell, K. E. *Can. J. Chem.* **1972**, *50*, 3304–3309.

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(22) Franz, J. A.; Barrows, R. D.; Camaioni, M. *J. Am. Chem. Soc.* **1984**, *106*, 3964–3967.

(23) Burton, A.; Ingold, K. U.; Walton, J. C. *J. Org. Chem.* **1996**, *61*, 3778–3782.

(24) The EPR spectrum of the reaction mixture showed strong signals due to the phenoxy radical from **2b**.

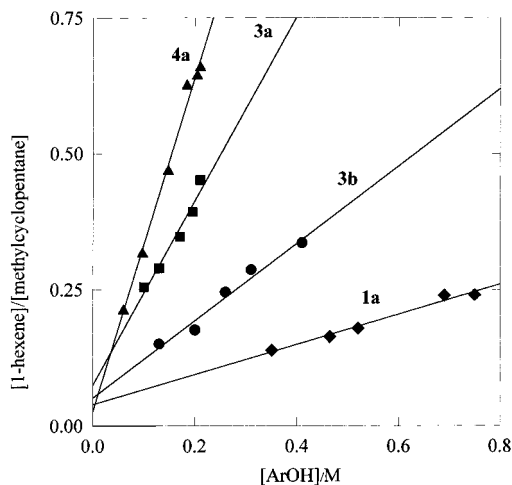


Figure 1. Concentration ratio of the unrearranged and rearranged hydrocarbons obtained in toluene at room temperature in the reaction of 5-hexenyl radical with phenols **1a**, **3a**, **3b**, **4a**.

– $10.83/(2.3RT)$,^{22,23} the intercept on the vertical axis was ca. 5. Thus, at low phenol concentration, the [UH]/[RH] ratio tends to a constant value that is not zero. This indicates that the reaction mixture contains a substance other than the phenol that is capable of donating hydrogen atoms to the neophyl radical in competition with its rearrangement. To check if the hydrogen donor was the solvent, measurements were repeated in the absence of any phenol, under which conditions the [UH]/[RH] ratio was 4.3. From this ratio we calculate that the rate constant for hydrogen atom abstraction by a primary alkyl radical from toluene (molarity of neat solvent, 9.4 M) is $k_H^{298} = 4.6 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ at room temperature.

For the strongly hindered 2,6-di-*tert*-butyl-4-methylphenol (**2a**) the [UH]/[RH] ratio did not depend on the phenol concentration (Figure 2a), which indicates that at the concentration of **2a** employed, transfer of its hydroxylic hydrogen atom to the neophyl radical is slower than transfer from toluene. Kinetic studies on the less reactive phenols with the neophyl radical were therefore carried out in benzene in which the [UH]/[RH] intercept ratio is ca. 0.7 (Figure 2b). This nonzero intercept is most probably due to hydrogen atom abstraction from the hexa-*n*-butylditin and (less probably) from the neophyl bromide.²⁵ All the rate constants measured at room temperature in the two aromatic solvents using two radical clocks are reported in Table 1.

The kinetics of the hydrogen atom transfer to alkyl radicals was also studied over a range of temperatures for three phenols, one without ortho substituents, 4-fluorophenol (**5e**), 2,4,6-trimethylphenol (**1a**), and 2,6-di-*tert*-butylphenol (**2c**). The measured ratios between the rate constants for hydrogen atom abstraction and rearrangement of the primary alkyl radicals are reported in Table 2. The absolute values of k_H could be obtained at various temperatures from the Arrhenius parameters for the two rearrangements (vide supra). Figure 3 shows, as an example, the experimental data for **2c**. The Arrhenius parameters for the three phenols are reported in Table 3.

Ingold and co-workers^{9–11} recently reported that hydrogen atom abstraction from phenols by cumyloxyl, *tert*-butoxyl, and DPPH radicals showed dramatic solvent effects in hydrogen bond accepting (HBA) solvents. We therefore decided to see whether similar effects occurred with alkyl radicals using six

solvents having very different HBA abilities, viz., isooctane, toluene, anisole, acetonitrile, *tert*-butyl alcohol, and γ -valerolactone.

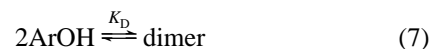
We studied α -tocopherol (α -TOH) more thoroughly because of its importance as a natural antioxidant. Hydrogen abstraction was studied at room temperature with use of concentrations of α -TOH ranging from 0.15 to 0.70 M. The 5-hexenyl radical clock was used in low HBA solvents and the neophyl radical in the high HBA solvents *tert*-butyl alcohol and γ -valerolactone, where the reactivity of the antioxidant is lower. The experimental data are collected in Table 4. Figure 4 shows that the rate constant for hydrogen abstraction decreases strongly as the HBA ability of the solvent increases.

Kinetic measurements with α -TOH were also carried out in isooctane/*tert*-butyl alcohol and isooctane/ γ -valerolactone solvent mixtures at various solvent compositions. Isooctane was chosen because it is not a HBA solvent. The dependence of the rate constant k_H on solvent composition is shown in Figure 5 and will be discussed later.

The importance of steric crowding around the hydroxyl group in relation to the interactions of phenols with HBA solvents was examined by measuring the kinetic solvent effect for 2,4,6-trimethylphenol (**1a**) and 2,6-di-*tert*-butylphenol (**2c**) in toluene and γ -valerolactone, and for the latter also in *tert*-butyl alcohol (see Table 4).

Phenols without Ortho Substituents. The behavior of phenols **5a–i** in their reactions with the radical clocks in benzene was different from that of the phenols discussed so far. Figure 6 shows, as an example, the dependence of the ratio [UH]/[RH] on the concentration of the unsubstituted phenol, **5a**, in benzene. The experimental points lie on a curve and the rate constant for hydrogen atom abstraction from **5a** decreases with an increase in the phenol concentration. Such apparently anomalous behavior can be attributed to self-association of phenol. The phenol concentration was always lower than 1 M in our measurements, and phenol dimers (eq 7) are expected to be the dominant aggregated species in solution.²⁶ Interestingly, nonlinearity of the plot [UH]/[RH] vs [ArOH] has not been observed with any *ortho*-substituted phenol presumably for steric reasons.

Self-association reduces the concentration of free, i.e., non-hydrogen bonded phenol, available for reaction with the radical clocks, and it is this that causes a decrease in the measured values of k_H with increasing phenol concentration.



The experimental data can be treated by using a model analogous to that proposed by Ingold and co-workers to interpret the kinetic solvent effect in the reaction of phenols with alkoxy, peroxy, and hydrazyl radicals (see Discussion).^{9–11} Thus, by assuming that only the free phenol reacts with the radical clock and that the dimer does not, we obtain eq 8 (where [ArOH]₀ is the total concentration of phenol and K_D the equilibrium constant for dimer formation).

$$k_H = a + k_r \frac{[\text{UH}]}{[\text{RH}]} \frac{4K_D}{(1 + 8K_D[\text{ArOH}]_0)^{1/2} - 1} \quad (8)$$

(25) One of the reviewers has suggested that alkylated benzene derivatives resulting from the addition of alkyl radicals to the solvent are the source of hydrogen atoms.

(26) (a) Maguire, M. M.; West, R. *Spectrochim. Acta* **1961**, *19*, 369–378. (b) Ciddel, V.; Becker, E. D. *Spectrochim. Acta* **1957**, *10*, 70. (c) Saunders, M.; Nyne, J. B. *J. Chem. Phys.* **1959**, *31*, 270. (d) Saunders, M.; Nyne, J. B. *J. Chem. Phys.* **1958**, *26*, 1319.

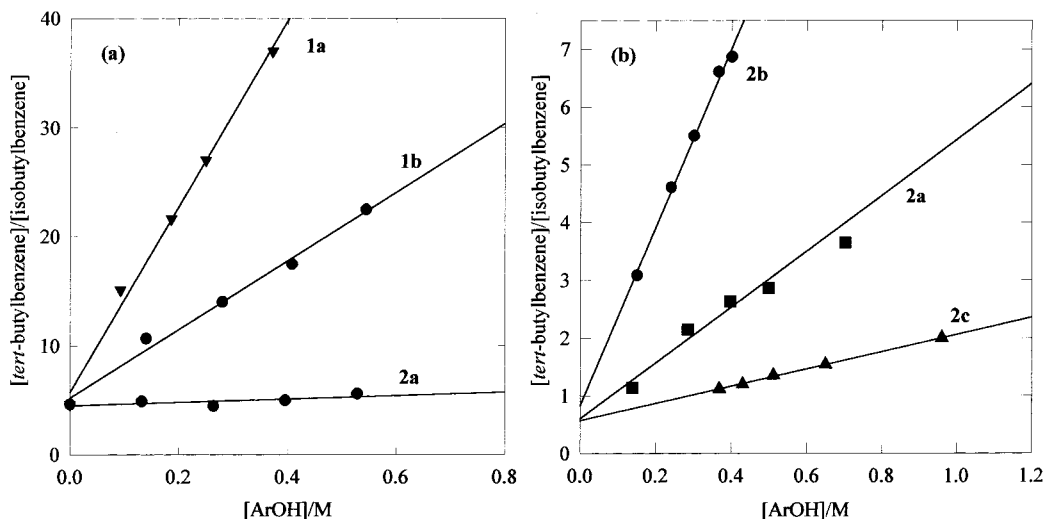


Figure 2. Concentration ratio of the unrearranged and rearranged hydrocarbons obtained at room temperature in the reaction of neophyl radicals with phenols **1a**, **1b**, **2a**, **2b**, **2c**. Plots (a) and (b) show the data obtained in toluene and in benzene, respectively.

Table 1. Absolute Rate Constants for the Abstraction of the Hydroxylic Hydrogen Atom from Phenols by Primary Alkyl Radicals at 298 K

phenol ^a	clock ^b	solvent ^c	$10^{-4}k_{\text{H}} \text{ (M}^{-1} \text{ s}^{-1})$ ^d
1a (0.35–0.75 M)	H	B	6.4 ± 1
1a (0.09–0.37 M)	N	T	8.5 ± 0.8
1b (0.14–0.54 M)	N	T	3.1 ± 0.4
2a (0.14–0.50 M)	N	B	0.48 ± 0.15
2b (0.15–0.40 M)	N	B	1.6 ± 0.13
2c (0.33–1.30 M)	N	B	0.25 ± 0.01
3a (0.10–0.21 M)	H	T	39 ± 9.1
3b (0.13–0.41 M)	H	T	16 ± 3.7
4a (0.06–0.21 M)	H	T	71 ± 7.3
4b (0.13–0.38 M)	H	T	60 ± 15
5a (0.10–1.25 M)	N	B	3.4 ± 0.8
5b (0.20–0.80 M)	N	B	5.3 ± 1.0
5c (0.10–0.80 M)	N	B	6.7 ± 1.1
5d (0.12–0.92 M)	H	B	23 ± 4.2
5e (0.10–0.81 M)	N	B	2.4 ± 0.5
5f (0.11–1.22 M)	N	B	3.0 ± 0.4
5g (0.10–0.69 M)	N	B	1.8 ± 0.5
5h (0.10–0.71 M)	N	B	0.44 ± 0.1
5i (0.04–0.10 M)	N	B	0.23 ± 0.15

^a The range of concentrations employed is given in parentheses. ^b H \equiv 5-hexenyl, N \equiv neophyl. ^c B \equiv benzene, T \equiv toluene. ^d Errors correspond to twice the standard deviation.

By fitting our experimental data to eq 8 (with a taken as 0.7 which corresponds to the intercept on the [UH]/[RH] vertical axis found in the absence of phenols) the curve shown in Figure 6 was obtained by using $k_{\text{H}} = 3.4 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ and $K_{\text{D}} = 3.99 \text{ M}^{-1}$. The latter value compares favorably with the value of 4.7 M^{-1} in CCl_4 reported in the literature.²⁶ To confirm our assumption that the nonlinear variation of the [UH]/[RH] ratio with phenol concentration is due to the formation of dimers, we repeated these measurements in benzene containing 1.04 M *tert*-butyl alcohol (a strong HBA solvent), which preferentially hydrogen bonds phenol and therefore reduces self-aggregates to a negligible amount. Under these conditions the plot of [UH]/[RH] vs phenol concentration is linear (see Figure 6).

Similar analyses were performed for the other phenols lacking *ortho* substituents. With **5b–d**, dimerization was found to be important in the examined concentration range and the obtained K_{D} values are reported in footnote 27. On the other hand, the K_{D} values determined for **5e–i** were smaller than the experi-

Table 2. Kinetic Data for the Reactions of the 6-Bromo-1-hexenyl Radical with 2,4,6-Trimethylphenol (**1a**) in Toluene and of the Neophyl Radical with 2,6-Di-*tert*-butylphenol (**2c**) and *p*-Fluorophenol (**5e**) in Benzene

phenol	$T, \text{ K}$	[phenol], ^a M	$k_{\text{H}}/k_{\text{t}}$, ^b M^{-1}
1a	294	0.35–0.73	0.28 ± 0.02
	319	0.35–1.4	0.20 ± 0.04
	338	0.35–1.4	0.13 ± 0.02
	358	0.35–1.4	0.097 ± 0.005
2c	294	0.33–1.3	2.45 ± 0.71
	305	0.36–0.96	1.49 ± 0.05
	319	0.35–1.4	0.97 ± 0.26
	338	0.35–1.4	0.47 ± 0.11
5e	358	0.35–1.4	0.28 ± 0.12
	298	0.10–0.50	22.2 ± 5
	313	0.10–0.50	13.0 ± 2.5
	328	0.10–0.50	6.8 ± 1.5
	343	0.10–0.50	4.2 ± 1
358	0.10–0.50	3.8 ± 1	

^a Range of concentrations employed. ^b Errors correspond to twice the standard deviation.

mental error, and therefore were neglected. The rate constants obtained in benzene for these phenols are reported in Table 1.²⁷

In the case of 4-fluorophenol, the Arrhenius parameters of the hydrogen abstraction reaction were also determined by taking measurements in the temperature range 25–85 °C (see Tables 2 and 3).

FT-IR Measurements. To check whether the kinetic data provide reliable equilibrium constants for the formation of hydrogen-bonded complexes, equilibrium constants were also measured by FT-IR, which allows both the free and hydrogen-bonded species to be observed. For example, Figure 7 shows the IR spectra of vitamin E recorded at room temperature, in the 3100–3750 cm^{-1} range, in isooctane and in a mixture of isooctane/ γ -valerolactone (0.54 M). In the former case, only the free phenol can be detected whereas in the solvent mixture both free (sharp peak) and complexed (broad peak) phenol were observed. Even in pure γ -valerolactone non-hydrogen bonded vitamin E is present in measurable quantities as indicated by a small IR peak at 3638 cm^{-1} . At an α -TOH concentration of 0.058 M in γ -valerolactone the integrated intensity of this peak is 2.5% of that observed in pure isooctane.

(27) The monomer–dimer equilibrium constants determined by numerical fitting of experimental data measured for phenols **5a–d** to eq 11 are the following: 3.99 (**5a**), 2.17 (**5b**), 2.88 (**5c**), and 15.9 (**5d**) M^{-1} .

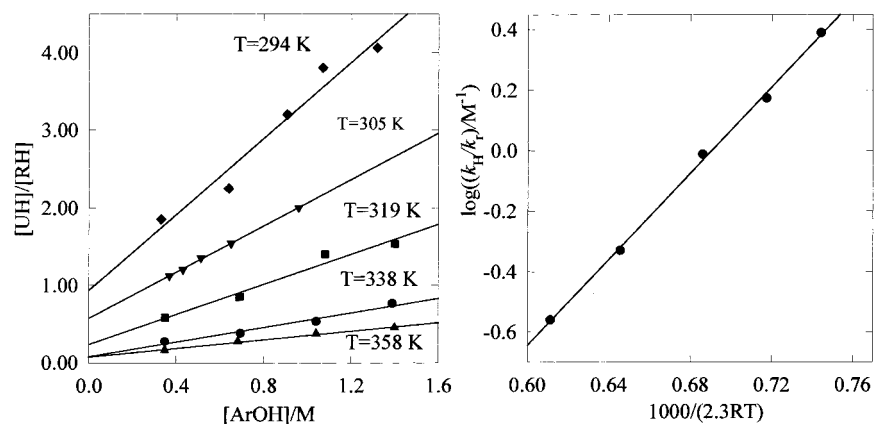


Figure 3. Measurements at various temperatures of k_H/k_r for **2c** and the corresponding Arrhenius plot.

Table 3. Arrhenius Parameters for the Hydrogen Atom Abstraction Reaction from Phenols by Primary Alkyl Radicals in Benzene

phenol	ortho groups	log A	E_a /kcal mol ⁻¹	k_H^{298} /M ⁻¹ s ⁻¹
5e	H	7.43	4.18	2.3×10^4
1a	Me	7.26	3.34	6.4×10^4
2c	CMe ₃	6.05	3.62	2.5×10^3

Table 4. Room Temperature (298 K) Absolute Rate Constants for the Abstraction of the Phenolic Hydrogen Atom of Substituted Phenols by Primary Alkyl Radicals (U^{*}) and by *tert*-Butoxyl Radicals Measured in Different Solvents, and Equilibrium Constants for the Formation of the Hydrogen Bonded Complex with Solvent, K^S , Determined by the Kinetic Method and by FT-IR Spectroscopy

phenol	solvent	$10^{-4}k_H$		$10^{-8}k_H$		K^S_{KIN}	K^S_{FT-IR}
		(U [*])	clock ^a	(Me ₃ CO [*]) ^b			
4b	isooctane	115.	H	99 ^c	$\sim 0^d$		
	toluene	59.6	H	31 ^e	0.10		
	anisole ^f	44.0	H	20	0.19		
	acetonitrile ^f	23.0	H	9.4	0.25		
	<i>tert</i> -butanol	3.2	N	1.8	3.7		
1a	γ -valerolactone	2.0	N	1.6	5.2	4.7	
	toluene	8.5	N				
2c	γ -valerolactone	0.44	N		6.7	7.8	
	toluene	0.30	N				
	<i>tert</i> -butanol	0.53	N		~ 0		
	γ -valerolactone	0.31	N		~ 0	~ 0	

^a H \equiv 5-hexenyl, N \equiv neophyl. ^b Taken from ref 11. ^c Value measured in *n*-pentane. ^d Assumed. ^e Value measured in benzene. ^f Due to the low solubility of 6-bromo-1-hexene in these solvents, some toluene (1 M) was added to the solutions.

Measurements were carried out by recording the IR spectra in five different mixtures of isooctane and γ -valerolactone and by evaluating the area of the absorbance peak due to the free phenol. The concentrations of the free α -TOH, obtained from these measurements (see Experimental Section) were plotted as a function of the concentration of γ -valerolactone to obtain the equilibrium constant for hydrogen bonding, K^S (concentration basis),²⁸ see Table 4.

Discussion

Rate constants for the hydrogen atom abstraction from 18 phenols by primary alkyl radicals at room temperature are collected in Table 1. These constants, which span the range from 2.3×10^3 M⁻¹ s⁻¹ for 4-cyanophenol to 7.1×10^5 M⁻¹ s⁻¹ for α -TOH, are larger in phenols containing electron-donating *para* substituents (H < Me < OMe) and smaller in phenols, such as

(28) Mills, I.; Cvitas, T.; Homann, K.; Kallay, N.; Kuchitsu, K. *Quantities, Units and Symbols in Physical Chemistry*; Blackwell: Oxford, 1993; p 50.

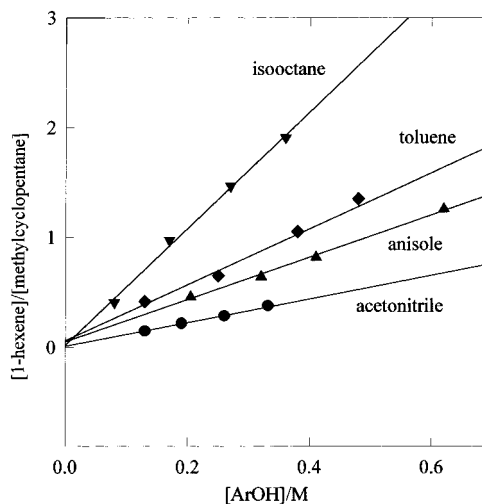


Figure 4. Determination of k_H for α -TOH (**4b**) in various solvents using the 5-hexenyl clock.

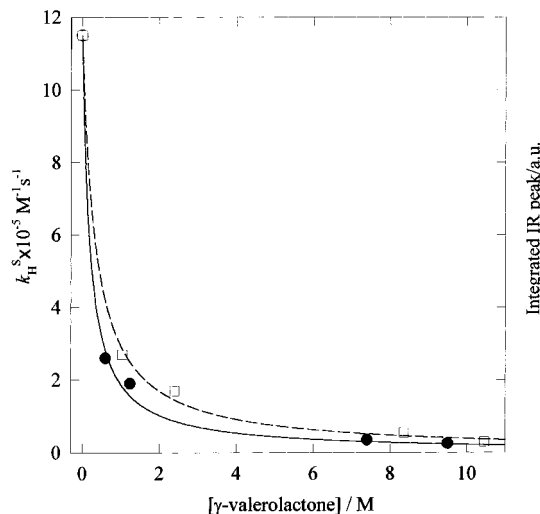


Figure 5. Determination of the equilibrium constant for hydrogen bonding of α -TOH (**2c**) to γ -valerolactone using kinetic (continuous line) and FT-IR data (dotted line).

5e–i, substituted with electron-withdrawing groups. Table 1 also shows that the rate constants decrease as the bulk of the *ortho* substituents increases along the series H < Me < CMe₃, confirming the well-known fact that steric factors have a big influence on the reactivity of phenols toward free radicals. That is, bulky *ortho* groups hinder the approach of an attacking radical

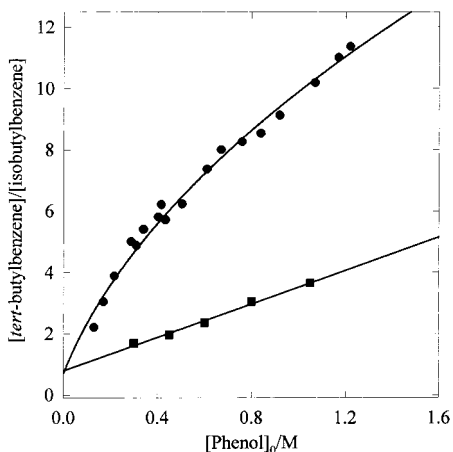


Figure 6. Plot of the product ratio versus concentration of phenol (**5a**) obtained in the reaction with neophyl radicals in benzene (●) and in a benzene solution containing 1.04 M *tert*-butyl alcohol (■).

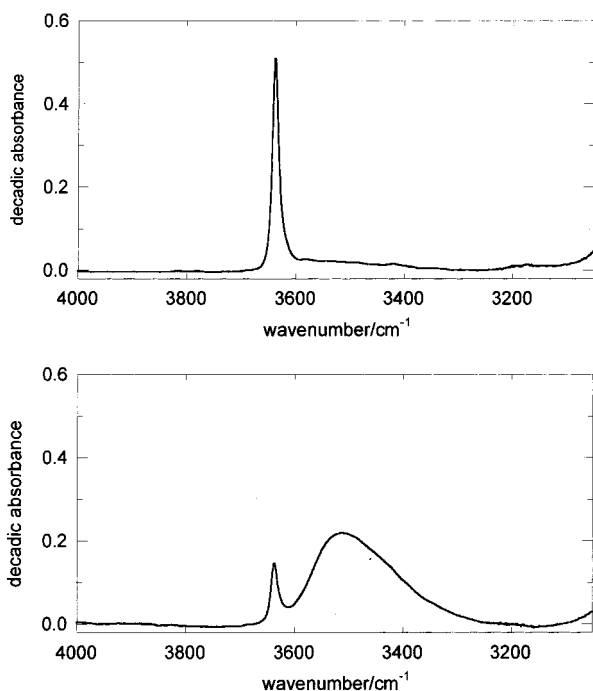


Figure 7. FT-IR spectra of 0.0058 M α -TOH (**2c**) in isooctane (upper) and a isooctane solution containing 0.54 M γ -valerolactone (lower).

and this effect is reflected by the log *A* values reported in Table 3 which decrease with increasing size of the *ortho* substituents.

The importance of electronic factors is revealed by the effect of *para* substituents. Electron-donating substituents are well-known to reduce O–H bond dissociation enthalpies (BDE'S) of phenol and electron-withdrawing substituents to increase O–H BDE's.^{29–31} This behavior can be understood in terms of the effect of the substituents on the stability of the phenoxyl radicals and of the parent phenols. Both donors and acceptors conjugatively stabilize aroxyl radicals,^{5,29} while an opposite effect is expected on the stability of the phenols. Electron-donating groups destabilize the starting phenol with respect to the parent unsubstituted compound (see structure B) because

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

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

(31) Pedrielli, P.; Pedulli, G. F. *Gazzetta* **1997**, *127*, 509–512.

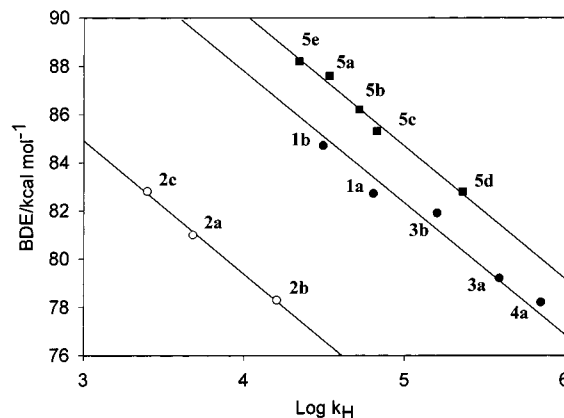
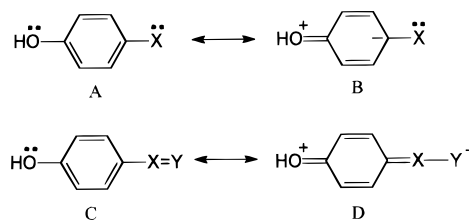


Figure 8. Plot of the O–H Bond Dissociation Energies versus log k_H for phenols containing in the two *ortho* positions hydrogens (■), methyl (●), and *tert*-butyl (○) groups.

of electrostatic repulsion between the negative charge delocalized in the aromatic ring and the electron-rich substituent. Electron-withdrawing substituents, on the other hand, increase the O–H BDE's by conjugatively stabilizing the phenol (structure D) more than its aroxyl radical.

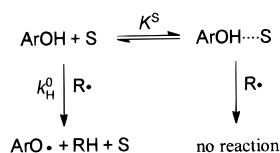


Excellent linear correlations are obtained when the logarithms of the room temperature rate constants for the H-atom abstraction by primary alkyl radicals are plotted against the O–H BDE's for the phenols,^{29–32} see Figure 8. All the data fall on one of three straight lines, one line for the phenols without *ortho* substituents and the other two lines for phenols containing two *ortho* methyl or two *ortho tert*-butyl groups. This implies that the activation energies for the H-atom transfer are proportional to the strength of the O–H bond being broken and, therefore, are inversely proportional to the exothermicity of the reaction. The three different lines obtained for the phenols bearing different *ortho* substituents have approximately the same slope but are displaced from each other because of entropic factors (see above). Thus, steric crowding about the hydroxylic group is very important in decreasing the reactivity of phenols and therefore in reducing their effectiveness as inhibitors of radical chain reactions. It should be emphasized that similar correlations were found some time ago by Howard and Ingold³ by plotting the logarithm of the room temperature rate constant for the reaction of peroxy radicals with variously substituted phenols with the sum of the σ^+ values of the substituents.

A comparison of the present data with the rate constants for hydrogen abstraction from phenols by peroxy radicals, reported by Ingold and co-workers,⁵ indicates, as expected, that the exothermicity of the H-transfer is not the only important factor determining the rates of these processes. The peroxy radical rate constants are about 2–3 times larger than those measured here despite the fact that the reaction of phenols with alkyl

(32) The previously unreported BDE value for the O–H bond in *p*-fluorophenol in benzene was measured as 88.1 kcal/mol by using the same procedure of ref 29.

Scheme 2



radicals is more exothermic by ca. 10 kcal/mol than the reaction with peroxy radicals.³³ The higher reactivity of peroxy radicals with phenols can be nicely rationalized on the basis of the magnitude of the triplet repulsion terms in the transition state for the H-transfer which will be lower for transfer between two oxygen atoms rather than between oxygen and carbon.³⁴

A special comment is deserved for 2,3,5,6-tetramethyl-4-methoxyphenol (**3b**) which, despite having a structure very similar to that of 2,3,6-trimethyl-4-methoxyphenol (**3a**), is characterized by a k_{H} value that is lower by a factor of 2.5. These anomalous data parallel the BDE's for these two compounds and can be attributed to the fact that in **3b** the methoxy group is approximately perpendicular to the plane of the aromatic ring for steric reasons and hence its oxygen atom's 2p lone pair cannot conjugate with the π system.^{4,5,29} In this geometry both the stabilization of the phenoxyl radical and the destabilization of the phenol by the *para* MeO substituent are substantially lost with a consequent increase of the activation energy for H-transfer with respect to **3a** where the OMe group is coplanar with the aromatic ring.

As far as the effect of solvents on the rate constants for hydrogen abstraction from phenols is concerned, Table 4 reports the experimental values for the reaction of α -tocopherol with alkyl radicals obtained in the present study together with those reported for the reaction of the same substrate with *tert*-butoxyl radicals. It can be seen that direction and magnitude of the solvent effect is the same for the two reactions despite the fact that the absolute k_{H} values differ by 4 orders of magnitude. In fact, a plot (not shown) of $\log k_{\text{H}}(\text{RO}\cdot)$ versus $\log k_{\text{H}}(\text{R}\cdot)$ is linear and has the expected¹¹ slope of 1. This provides additional evidence that kinetic solvent effects for hydrogen atom abstraction from phenols are totally independent of the nature of the attacking radical and are due solely to hydrogen bond formation between solvent and the phenolic substrate.

The dependence of the measured values of k_{H} on solvent composition in mixtures of isooctane and *tert*-butyl alcohol or γ -valerolactone (Figure 5) can be analyzed in terms of the simple model proposed by Ingold and co-workers. This model is based on the following assumptions: (i) solvent, S, and substrate, ArOH, can give rise only to 1:1 hydrogen-bonded complexes, ArOH \cdots S, and the equilibrium constant for complexation, K^S , is independent of the nature of the surrounding medium; (ii) the attacking radicals react with the free phenol with a rate constant k_{H}^0 , but not with the complexed phenol (see Scheme 2) since, for steric reasons, they cannot approach the solvent-bonded hydroxylic hydrogen atom. The rate constant, k_{H}^0 , for reaction with free phenol is the value in a hypothetical solvent where no substrate-solvent interaction occurred.

The equilibrium constant is given by:

$$K^S = \frac{[\text{ArOH}\cdots\text{S}]}{[\text{ArOH}]_{\text{free}}[\text{S}]} \quad (9)$$

and, by definition,

$$k_{\text{H}}^S[\text{ArOH}]_{\text{total}} = k_{\text{H}}^0[\text{ArOH}]_{\text{free}}$$

the measured rate constant can be expressed (eq 10) as a function of K^S and of the concentration of the HBA solvent. This equation implies that K^S can be calculated from k_{H}^0 and k_{H}^S .

$$k_{\text{H}}^S = \frac{k_{\text{H}}^0}{1 + K^S[\text{S}]} \quad (10)$$

The value assumed for k_{H}^0 was that measured in pure isooctane ($1.15 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$). The k_{H}^S values, plotted against the molar concentrations of the HBA, were fitted to eq 10 to obtain K^S (see Figure 5). The resulting room temperature values of K^S for the formation of the hydrogen-bonded complex between α -TOH and the HBA were 3.7 M^{-1} for *tert*-butyl alcohol and 5.2 M^{-1} for γ -valerolactone (see Table 4).

For γ -valerolactone the equilibrium constant, K^S , was determined by FT-IR by fitting the experimental concentrations of free α -TOH to eq 11. The resulting value of the equilibrium constant, $K^S = 4.7 \text{ M}^{-1}$, is in excellent agreement with that obtained from the kinetic data (5.2 M^{-1}).

$$[\text{ArOH}]_{\text{free}} = \frac{[\text{ArOH}]_{\text{tot}}}{1 + K^S[\text{S}]} \quad (11)$$

Since the kinetic and the IR methods give comparable results, we conclude that measurements of the rate constants for hydrogen atom abstraction using radical clocks represents a new and reliable technique for the determination of equilibrium constants for hydrogen bonding by phenols and, presumably, by other hydrogen bond donating substrates. This technique is especially useful with those solvents, such as alcohols and amines, for which the IR method cannot be used because of the strong absorption in the 3300–3600 cm^{-1} spectral region.

The kinetic data obtained in toluene and γ -valerolactone for 2,4,6-trimethylphenol (**1a**) and 2,6-di-*tert*-butylphenol (**2c**) (Table 4) indicate that the kinetic solvent effect for **1a** is large and comparable to that for α -TOH whereas it is negligible for **2c**. This implies that solvation of the hydroxylic hydrogen atom is about the same in the two *ortho* dimethyl substituted phenols but is unimportant in the di-*tert*-butyl substituted phenol because of the large steric hindrance due to these bulky groups.³⁵ IR spectroscopic data support this view; in fact, the vibrational spectra of **2c** show in the region of the free O–H absorption a sharp peak at 3640 cm^{-1} having the same intensity in pure isooctane and pure γ -valerolactone, indicating that no hydrogen bonding occurs in either solvent. Analogous IR experiments carried out with **1a** in γ -valerolactone give $K^S = 7.80 \text{ M}^{-1}$, a value only slightly higher than that of α -TOH, due to the higher acidity of **1a**.

Experimental Section

Materials. Solvents were of the highest purity grade commercially available and were used as received. Phenol, 4-chlorophenol, 4-bromophenol, 4-fluorophenol, 4-cyanophenol, 4-trifluoromethylphenol, 4-methoxyphenol, 4-methylphenol, and 4-*tert*-butylphenol were purchased from Aldrich and were used as received. 2*R*,4*R*,8*R* (*d*)- α -tocopherol (Aldrich) was purified by column chromatography on silica gel according to a previously described method.¹¹ All other phenols were available from previous studies²⁹ and were purified by crystal-

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(34) Zavitsas, A. A. *J. Am. Chem. Soc.* **1972**, *94*, 2779–2789. Zavitsas, A. *J. Am. Chem. Soc.* **1991**, *113*, 4755.

(35) The failure of 2,6-di-*tert*-butylphenols to form hydrogen bonds was originally recognized in the early sixties. See for instance: Ingold, K. U. *Can. J. Chem.* **1960**, *38*, 1092. Ingold, K. U.; Taylor, D. R. *Can. J. Chem.* **1961**, *39*, 471. Ingold, K. U. *Can. J. Chem.* **1962**, *40*, 111.

lization from a suitable solvent (generally hexane). Hexa-*n*-butylditin and 6-bromo-1-hexene (Aldrich) were stored under nitrogen at 5 °C. Di-*tert*-butylperoxide (98% pure, from Aldrich) was percolated through activated basic alumina and stored at 5 °C. Neophyl bromide was prepared from neophyl chloride according to the literature.³⁶

Kinetic Measurements. In a typical experiment 200 μL of a solution of the phenol (0.1–1 M) containing either neophyl bromide or 6-bromo-1-hexene (0.005–0.01 M) and hexa-*n*-butylditin (0.01 M) were sealed in a quartz tube, after being deoxygenated by bubbling nitrogen. The reaction mixtures were then irradiated for 30–120 min at the desired temperature in a thermostated 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, 4 to 7 measurements were made with different phenol concentration, and the reaction products ratio $[\text{UH}]/[\text{RH}]$ was plotted versus the phenol concentration to obtain the $k_{\text{H}}/k_{\text{r}}$ ratio by linear regression of the experimental data.

For self-associating phenols 10 to 20 measurements with different $[\text{ArOH}]_0$ were made and the experimental data were fitted to eq 8.

With neophyl bromide, in some cases, it was not possible to obtain a good chromatographic resolution between the phenol and the reaction products. These reaction mixtures were analyzed by GC-MS by using the Single Ion Monitoring (SIM) detection mode at m/z^+ 91 and 119, after calibration of the spectrometer response with authentic samples of isobutylbenzene and *tert*-butylbenzene.

FT-IR Measurements. All the FT-IR spectra were measured from 4000 to 3000 cm^{-1} with a Bruker IFS 113v, which operates “in a vacuum”, that is at about 15 mbar N_2 , a strictly reproducible instrumental atmosphere, resolution 1 cm^{-1} , apodization function 3-terms Blackman-Harris, 64 scans. The cell used^{37,38} was 500 μm thick with CaF_2 windows, and was completely disassembled and cleaned after each measurement. All the samples were prepared in containers just larger than the final volume and previously filled with argon. Volumetric measurements were carried out with Hamilton gastight syringes and a

Schott 10 mL precision volumetric flask—the former having a precision verified equal to or better than 1%, the latter a precision of 0.2%.

The absorbance spectrum of the phenol was obtained by subtracting from the spectrum of the solution the absorbance of the solvent multiplied by its volume fraction and, when present, the absorbance of the proton acceptor multiplied by its stoichiometric, or initial, volume fraction. In the approximation of linear additivity of absorbance spectra,^{38,39} such volume fractions should be evaluated from the *partial* molar volumes in solution, which were not available. Instead, as an approximation, we used the molar volume, the ratio of the molar weight, and density. The latter was determined by weighing a gas-tight syringe filled with the species of interest; for 2,4,6-trimethylphenol and 2,6-di-*tert*-butylphenol we found 1.01 and 0.92 g mL^{-1} , respectively.

The integrated decadic molar extinction coefficient of free **1a** was 146 $\text{cm}^2 \text{mol}^{-1} \text{dm}^3$. The equilibrium constant for complexation by γ -valerolactone was obtained by measuring the intensity of the free phenol absorption in five different mixtures of isooctane and γ -valerolactone.

The extinction coefficient of free vitamin E ($\epsilon = 96.7$) was determined in pure isooctane by using dilute solutions (from 0.01 to 0.05 M). At higher concentrations ($[\alpha\text{-TOH}] > 0.2 \text{ M}$) the integrated absorbance starts to deviate from linearity with $[\alpha\text{-TOH}]$ due to self-association. The assumption that the extinction coefficient of the free phenol is not affected by the presence of the surrounding, but not hydrogen bonded, γ -valerolactone molecules was made when calculating the K^{S} values. The integrated absorption intensity was calculated only for the band at about 3640 cm^{-1} attributed to the non-hydrogen bonded species.

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