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Bond Dissociation Enthalpy of α-Tocopherol and Other Phenolic Antioxidants

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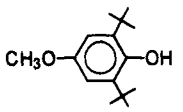
The equilibrium constants, K_1, for the reaction between galvinoxyl and a series of phenolic antioxidants have been determined by means of EPR spectroscopy. With aroxyl radicals decaying at appreciable rates, K_1 was obtained by performing kinetic analyses of the time dependence of the concentrations of the equilibrating radicals after mixing the reactants. In two cases the temperature dependence of K_1 was also studied and the entropy change for the equilibration reaction was determined. Bond dissociation enthalpies, DH, of the ArO—H bond of the examined phenols were calculated by comparison with the known value of 2,4,6-tri-*tert*-butylphenol (81.24 kcal mol^{-1}). A larger than expected DH value was found for probucol (81.03 kcal mol^{-1}) and an explanation of this behavior was given in terms of the preferred conformation adopted by the *para* alkylthio group. The DH value of α-tocopherol (78.93 kcal mol^{-1}) was found to be very close to that of the phenolic precursor of galvinoxyl (78.80 kcal mol^{-1}) and somewhat larger than that of 2,6-di-*tert*-butyl-4-methoxyphenol (77.61 kcal mol^{-1}).

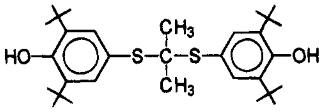
The determination of the O—H bond dissociation enthalpies, DH(ArO—H), of phenolic molecules is of considerable practical interest since this class of chemical compounds includes most of the synthetic and naturally occurring antioxidants which exert their action *via* an initial hydrogen transfer reaction whose rate constant depends on the strength of the O—H bond.

There are many reports in the literature of the determination of DH of phenols; those based on calorimetric, kinetic, and EPR methodologies have been reviewed by Denisov *et al.*[1] Recently, values determined with two new methods have been reported: one is based on a photoacoustic technique[2] while the other makes use of thermodynamic cycles by combining the heat of heterolysis of a given species and the redox potentials of the resulting ions.[3] Disappointingly the agreement between the values measured with the various techniques is poor; for instance, for phenol, the reported DH(ArO—H) spans the range from[2] 84.0 to[3] 91.6 kcal mol^{-1}.

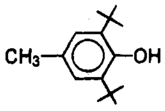
In the present investigation we report the determination of the bond dissociation enthalpies of the O—H bond in several substituted phenols of particular interest as antioxidants. The examined compounds include 2,6-di-*tert*-butyl-4-methoxyphenol (**1a**), probucol (**2a**), 2,6-di-*tert*-butyl-4-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)cyclohexa-2,5-dienone (**3a**), 2,6-di-*tert*-butyl-4-methylphenol (**4a**), and α-tocopherol (**5a**). These determinations have been made by means of EPR spectroscopy by measuring the equilibrium constant for the reaction between galvinoxyl (**3b**) and one of the above phenols, ArOH (eq 1).



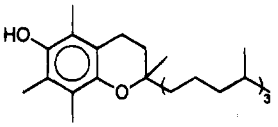
1a



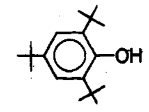
2a



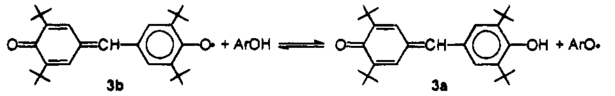
4a



5a



6a



(1)

All bond dissociation enthalpies were measured relative to that of 2,4,6-tri-*tert*-butylphenol (**6a**) whose DH value for the O—H bond is known from calorimetric studies as 81.24 ± 0.08 kcal mol^{-1}.[4,5]

All experiments were performed by measuring by EPR the absolute concentrations of the two radicals observed after mixing solutions of galvinoxyl and of a given phenol. Although for some of these antioxidants analogous experiments have been previously reported, they are sometime invalidated by the fact that other reactions,

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[®] Abstract published in *Advance ACS Abstracts,* July 1, 1994.

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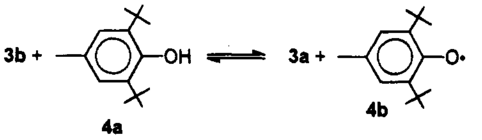
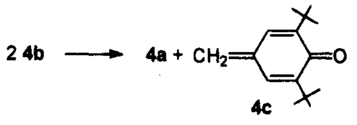
Table 1. Equilibrium Constants and Thermodynamic Parameters for Reaction 1

ArOH	solvent[a]	$K_1 \times 10^2$ (298 K)	ΔG°_1 (298 K) (kcal mol^{-1})	ΔH°_1 (kcal mol^{-1})	ΔS°_1 (cal mol^{-1} K^{-1})	DH (kcal mol^{-1})
1a	T	342 ± 35	−0.73 ± 0.07	−1.19 ± 0.10	−1.65 ± 0.35	77.61 ± 0.39
2a	T	2.32 ± 0.55	2.23 ± 0.13	(2.23 ± 0.13)[b]	nm[c]	81.03 ± 0.42
3a	T	100	0	0	0	78.80 ± 0.29
4a	B	4.03 ± 0.33	1.90 ± 0.05	(1.90 ± 0.05)[b]	nm	80.70 ± 0.34
5a	B	80 ± 12	0.13 ± 0.10	(0.13 ± 0.10)[b]	nm	78.93 ± 0.39
6a	T	1.17 ± 0.11	2.64 ± 0.07	2.44 ± 0.20	−0.71 ± 0.63	81.24 ± 0.08[d]

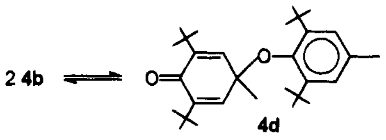
[a] B = benzene, T = toluene. [b] ΔH° is assumed equal to ΔG°. [c] Not measured. [d] From ref 4.

besides reaction 1, take place when mixing an aroxyl radical and a phenol. For instance, in the case of **4a** these reactions are the disproportionation of ArO•, affording benzoquinone methide and the starting phenol (eq 2), and the reversible formation of the head-to-tail dimer of the phenoxyl (eq 3); this, in turn, may decay to stable non-radical products (eq 4).





(2)



(3)

$$\mathbf{4d} \rightleftharpoons \mathbf{4a} + \mathbf{4c} \qquad (4)$$

Results and Discussion

Long Lived Phenoxyl Radicals. The determination of the equilibrium constants in the case of the couples galvinoxyl/2,6-di-*tert*-butyl-4-methoxyphenol (**1a**), galvinoxyl/probucol (**2a**), and galvinoxyl/2,4,6-tri-*tert*-butylphenol (**6a**) was straightforward since all the phenoxyl radicals derived from these phenols did not combine reversibly to give dimers and decayed slowly enough to allow the determination of their relative concentrations to be made directly (compounds **1a** and **6a**) or by extrapolation at zero time after mixing (compound **2a**).

Since all measurements were done by reacting the stable galvinoxyl radical (**3b**) with one of the above-mentioned phenols, we determined at first the equilibrium constant for the reaction of **3b** with **6a** for which the value of the O—H bond dissociation enthalpy in benzene is known as 81.24 ± 0.08 kcal mol^{-1}.[4,5] Mixing a deoxygenated toluene solution of **3b** (from 9×10^{-5} to 2.3×10^{-4} M) and of **6a** (from 3×10^{-3} to 8×10^{-3} M), led to the simultaneous observation of **3b** and of the 2,4,6-tri-*tert*-butylphenoxyl radical (**6b**). Integration of the overall spectrum, i.e. that due to both species, showed that when correcting for the dilution factor, the total radical concentration after mixing was practically coincident with that of the starting galvinoxyl and remained constant in time. On this basis the determination of the concentration of **3b** was simply done by measuring the decrease of the height of a nonoverlapping line of its EPR spectrum and that of **6b** by substracting this value to the initial radical concentration. At room temperature K_1 turned out to be $(1.17 \pm 0.11) \times 10^{-2}$ (see Table 1).[6]

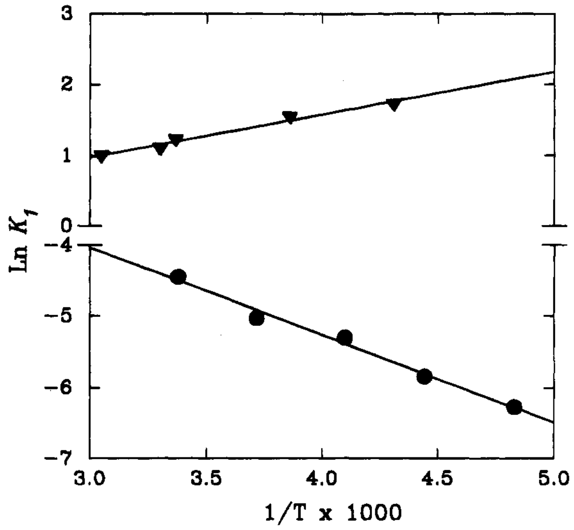


Figure 1. van't Hoff plots for the equilibria (●) **3b** + **1a** ⇌ **3a** + **1b** and (▼) **3b** + **6a** ⇌ **3a** + **6b**.

In order to determine the standard enthalpy change for the reaction of **3b** with **6a**, the equilibrium constant K_1 was determined over the range of temperatures from 217 to 298 K. The thermodynamic constants for reaction 1 were obtained from the integrated van't Hoff equation (eq 5) where ΔH°_1 and ΔS°_1 were assumed to be independent of temperature over the examined range. By plotting $\ln K_1$ vs. $1/T$ (see Figure 1) a good straight line ($r = 0.989$) was obtained, from which $\Delta H^\circ_1 = 2.44 \pm 0.20$ kcal mol^{-1} and $\Delta S^\circ_1 = -0.71 \pm 0.63$ cal mol^{-1} K^{-1} were derived. Since the O—H bond dissociation enthalpy of the phenol **3a** is related to that of **6a** (81.24 kcal mol^{-1}) and to ΔH°_1 by eq 6, we obtained DH(**3b**—H) as 78.80 ± 0.29 kcal mol^{-1}.

$$\ln K_1 = -\frac{\Delta H^\circ_1}{RT} + \frac{\Delta S^\circ_1}{R} \qquad (5)$$

$$\mathrm{DH}(\mathbf{3b}\text{—H}) = \mathrm{DH}(\mathbf{6b}\text{—H}) - \Delta H^\circ_1 \qquad (6)$$

When mixing deoxygenated toluene solutions of galvinoxyl and probucol (**2a**), the total radical concentration decreased gradually with time and also the radical ratio showed small changes. In the present case the concentrations required for the simultaneous observation of both radical species were in the range 6×10^{-5}–3×10^{-4} M for **3b** and 5×10^{-4}–2×10^{-3} M for **2a**. Extrapolation at zero time after mixing afforded the equilibrium

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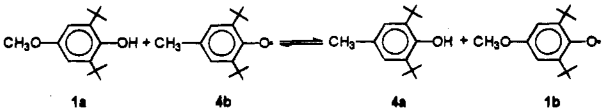
(6) The uncertains in the rate constants are reported as standard errors in the mean and have been adjusted for the sample size by multiplying by the Student *t* parameter for a 95% confidence interval.

constant K_1 at 298 K as $(2.32 \pm 0.55) \times 10^{-2}$ after correcting for the statistical factor due to the presence of two OH groups in probucol. The possible formation of the biradical from **2a** is believed to be negligible since under the above conditions only a small fraction of the diphenol (ca. 3%) was oxidized to the phenoxyl radical. If neglecting entropic effects, the O—H bond dissociation enthalpy of probucol is calculated as 81.03 ± 0.42 kcal mol^{-1}.

In the reaction of galvinoxyl with 2,6-di-*tert*-butyl-4-methoxyphenol (**1a**), no appreciable decay of the EPR signals was instead observed even several minutes after mixing the reactants. This favorable feature, reported also by other authors,[7] was exploited to perform a series of measurements at different temperatures (from 232 to 327 K) in order to determine the thermodynamic parameters for the equilibrium reaction 1 (see Figure 1). These were found to be $\Delta H°_1 = -1.19 \pm 0.10$ kcal mol^{-1} and $\Delta S°_1 = -1.65 \pm 0.35$ cal mol^{-1} K^{-1}, from which a DH value for the O—H bond in **1a** of 77.61 ± 0.39 kcal mol^{-1} was obtained.

It is worth pointing out that for the reaction of **3b** with both **1a** and **6a** the entropy change is quite small (<2 cal mol^{-1} K^{-1}). This contrasts with the result of a similar study carried out on the equilibration reaction between **1a** and **4b** (eq 7), where from the equilibrium constants measured at three different temperatures a value of $\Delta S°_7 = -10.04 \pm 2.63$ cal mol^{-1} K^{-1} was obtained.[8] This very large reduction of entropy was interpreted by admitting that while in phenol **1a**, the methoxy group is capable of free rotation, this is effectively stopped in the radical **1b** if maximum overlap of the π system with consequent stabilization is to be maintained. On the other hand, the *para* methyl group is free to rotate both in the phenol **4a** and in the phenoxyl radical **4b** since the stabilization of the latter one is independent of the orientation of the methyl group.[8]



(7)

By combining the data of our experiments we could calculate the entropy change for the equilibration of **1a** with **6b** (eq 8) as −0.94 ± 0.95 cal mol^{-1} K^{-1} which can be compared with the ΔS° value of −10.04 cal mol^{-1} K^{-1} for reaction 7, if it is assumed that the contribution to the entropy difference due to the rotation of the alkyl group (methyl or *tert*-butyl) in the phenol and phenoxyl radical is negligible.

$$\mathbf{1a} + \mathbf{6b} \rightleftharpoons \mathbf{1b} + \mathbf{6a} \qquad (8)$$

We believe that the much smaller entropy loss found in the present investigation is more likely for the following reasons. When radical **4b** is one of the equilibrating species, the concomitant reactions analogous to 2, 3, and 4 are of considerable importance and must be taken into account for the correct determination of the equilibrium constant; this does not seem to have been done by the authors of the above paper. Moreover, the ΔS° value of −10.04 cal mol^{-1} K^{-1} is exceedingly distant from an estimate of the change of entropy involved in reaction 7 that we have performed on the basis of Benson's rules.[9] ΔS° was calculated by assuming that the loss of entropy in reaction 8 is totally due to the reduced possibility of rotation of the methoxy group of **1a** around the oxygen—aryl bond on passing from the phenol to the phenoxyl radical. To determine the entropy contribution of the hindered rotation, we estimated the partition function Q_f for the free rotor OCH$_3$, in the approximation that it is connected to an infinite mass, by using eq 9, where I_r is the moment of inertia (amu Å^2) and σ is the internal symmetry number of the rotor.

$$Q_f = \frac{3.6}{\sigma}\left[I_r\frac{T}{300}\right]^{1/2} \qquad (9)$$

The decrease of entropy of the free rotor is a function of Q_f, of temperature, and of the rotational barrier, V_2, of the methoxy group. This barrier was reported to be 4.8 kcal mol^{-1} for the 4-hydroxyphenoxyl radical, which is a model system for **1b**, and 3.5 kcal mol^{-1} for the corresponding 1,4-dihydroxybenzene.[10,11] From these values we estimated, at 298 K, a loss of entropy due to the reduced rotational freedom in the radical of only 0.4 cal mol^{-1} K^{-1}. This suggests that the decrease of entropy due to the more hindered rotation in the phenoxyl radical is quite small; even in the unlikely case that the difference between the rotational barriers of the methoxy group in the phenol and phenoxyl radical is of the order of 10 kcal mol^{-1} the rotational contribution due to the loss of entropy cannot exceed ca. 2 cal mol^{-1} K^{-1}.

Reactive Phenoxyl Radicals. 2,6-Di-*tert*-butyl-4-methylphenol (4a). With **4a** the determination of the equilibrium constant for reaction 1 was not so straightforward since the phenoxyl radical **4b** is both in equilibrium with its dimer and decays irreversibly to diamagnetic products. In fact, after mixing galvinoxyl and **4a** the total amount of paramagnetic species present in solution decreased suddenly and then the remaining signals decayed slowly. This was interpreted by admitting fast equilibration with the dimer (eq 3) followed by slow decay of the phenoxyl radical *via* either a disproportionation reaction (eq 2) or through the intermediation of the dimer (eq 4). The equilibrium constant of reaction 1 (ArOH = **4a**) can be easily derived by following the decay of **3b** and **4b**, if the kinetic constants for reaction 2, 3, and 4 are known. Reactions 2−4 and their relative importance have been discussed in the literature and values of the rate and equilibrium constants were measured;[12] however they are too scattered to be useful. For instance, $K_3 = k_3/k_{-3}$ values ranging from 6×10^4 to 1.4×10^6 M^{-1} are reported at room temperature. Values considerably different of the rate constants for the irreversible decay of the phenoxyl **4b**, i.e. disproportionation of the radical (k_2) and fragmentation of the dimer (k_4), can also be found;[12] there is not even agreement about which of the latter two is the more important mechanism.[13,14] Since we could not rely on the literature data we repeated the kinetic study of the decay of the

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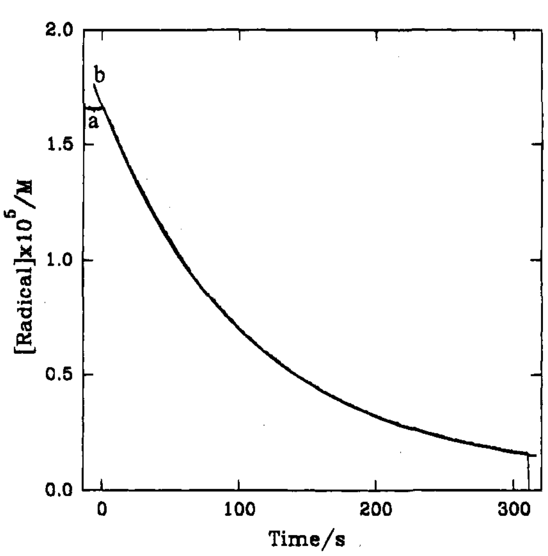

Figure 2. Experimental (a) and calculated (b) decay of radical **4b**.

aroxyl **4b**. Measurements were done in benzene or toluene in the range of temperatures 274–350 K, by producing the radical **4b** within the EPR cavity by photolysis of degassed solutions of the phenol **4a** containing some di-*tert*-butyl peroxide. A typical trace of the decay of **4b** observed when cutting off the light is shown in Figure 2. These traces obeyed first or second order or even mixed order kinetics, depending on the experimental conditions, i.e. initial radical concentration and temperature. This behavior, which is not uncommon in the kinetics of free radical reactions, has been widely discussed by Weiner and Mahoney[13] and by Ingold *et al.*[15] and can be explained in terms of either of the two kinetic schemes reported below. The former implies fast equilibration between the phenoxyl radical and its dimer followed by unimolecular decomposition of the latter one (eq 10).

$$2\mathrm{R}^\bullet \underset{\text{fast}}{\overset{K_3}{\rightleftharpoons}} \mathrm{R}_2 \xrightarrow{k_4} \text{products} \tag{10}$$

$$-\mathrm{d}[\mathrm{R}^\bullet]/\mathrm{d}t = 2k_4K_3[\mathrm{R}^\bullet]^2/(1 + 4K_3[\mathrm{R}^\bullet]) \tag{11}$$

The second scheme instead implies bimolecular disproportionation of the radical which is in equilibrium with a metastable dimer (eq 12).

$$\text{products} \xleftarrow{k_2} 2\mathrm{R}^\bullet \underset{\text{fast}}{\overset{K_3}{\rightleftharpoons}} \mathrm{R}_2 \tag{12}$$

$$-\mathrm{d}[\mathrm{R}^\bullet]/\mathrm{d}t = 2k_2[\mathrm{R}^\bullet]^2/(1 + 4K_3[\mathrm{R}^\bullet]) \tag{13}$$

When $4K_3[\mathrm{R}^\bullet] \gg 1$, the decay obeys first-order kinetics with $k_{\mathrm{obs}} = k_4/2$ in the former case and $k_{\mathrm{obs}} = k_2/(2K_3)$ in the latter one. On the other hand, if $4K_3[\mathrm{R}^\bullet] \ll 1$, second-order decay is expected with $k_{\mathrm{obs}} = 2k_4K_3$ and $k_{\mathrm{obs}} = 2k_2$, respectively, while mixed-order kinetics will be observed when $4K_3[\mathrm{R}^\bullet]$ is close to 1. Disappointingly, from the analysis of the decay traces it was not possible to decide which of the two schemes is more appropriate since the experimental curves were reproduced with either model.

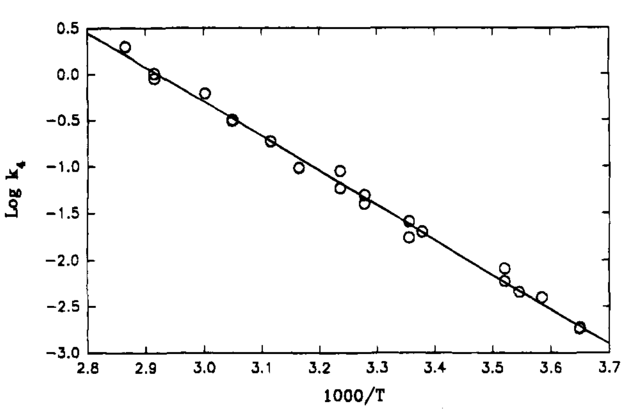

Figure 3. Plot of $\log(k_4/\mathrm{s}^{-1})$ vs $1/T$ for reaction 4.

To solve this problem we proceeded as follows: at first we choose experimental conditions such as to have mixed-order kinetics and analyzed the decay traces by numerical integration of the differential equations 11 and 13 (Runge–Kutta–Fehlberg method). Under these conditions the equilibrium constant K_3 could be determined irrespective of the mechanism of decay. An example of the quality of the fitting obtained by this procedure is shown in Figure 2. Mixed-order kinetics was found in the temperature range 296–320 K by starting with a steady-state concentration of the phenoxyl radical **4b** lying in the range 5×10^{-6}–1.5×10^{-5} M. At 296 K we found $K_3 = (3.7 \pm 1.2) \times 10^5$ M^{-1} and at 309 K $K_3 = (9.7 \pm 2.1) \times 10^5$ M^{-1}. These values are in good agreement with those calculated on the basis of the thermodynamic parameters for the equilibrium (3) reported by Levin *et al.*,[16] i.e. $\Delta S° = -33.98$ cal mol^{-1} K^{-1} and $\Delta H° = -17.49$ kcal mol^{-1}. The latter data, besides being in agreement with our values, are the result of a very careful study performed by means of a flash photolysis technique and have been used for the calculation of K_3 in the rest of this work, that is under experimental conditions where clean first- or second-order decay of **4b** was observed, in which the value K_3 could not be determined experimentally.

In the following step the disappearance of the phenoxyl radical was followed below 296 K or above 320 K where first- or second-order kinetics, respectively, were obeyed. From the values of k_{obs} and K_3, the rate constants k_2 and k_4 could be determined at various temperatures. In order to decide which of the two mechanisms described by eq 10 or 12 is more realistic, k_2 and k_4 were plotted in an Arrhenius diagram. The activation parameters obtained in the two cases are $E_2 = -0.41$ kcal mol^{-1} and $\log(A_2/\mathrm{mol}^{-1}\,\mathrm{s}^{-1}) = 3.48$ and $E_4 = 17.03$ kcal mol^{-1} and $\log(A_4/\mathrm{s}^{-1}) = 10.88$ (see Figure 3). An examination of these data shows that the parameters for the disproportionation of **4b** (eq 2) are out of any reasonable range and therefore we may conclude that the route of decay of **4b** is dimerization and subsequent decomposition of the dimer (eq 10).[17] A preference for the latter pathway has been stated by Weiner and Mahoney[13] while Parnell and Russell[14] surprisingly proposed the alternative mechanism (eq 12).

The overall kinetic scheme which should be considered when trying to determine the equilibrium constant for

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[17] One of the referees has suggested that the decomposition of the dimer to give stable products might take place *via* fragmentation to give two aroxyl radicals followed by disproportionation of the radicals in the solvent cage.

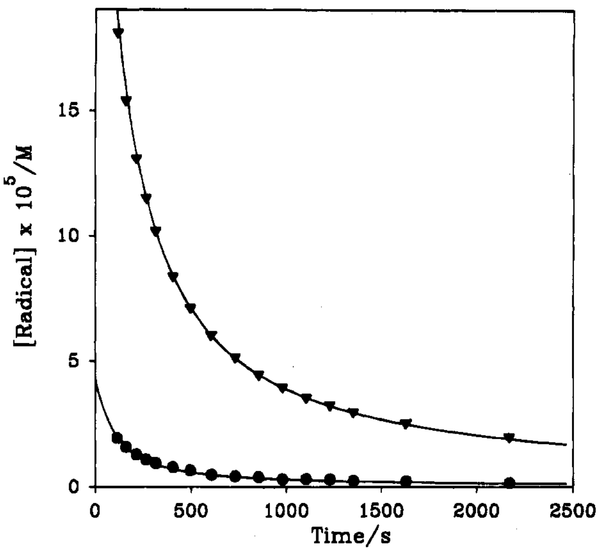


Figure 4. Decay of **3b** (▼) and **4b** (○) generated by mixing **3b** (7.88 x 10^{-4} M) and **4a** (2.00 x 10^{-3} M) in benzene.

the reaction of galvinoxyl (**3b**) with **4a** includes eqs 1 (ArOH = **4a**), 3, and 4. The reversible cross combination of **3b** with **4b** which may also represent a possible reaction has been neglected (*vide infra*). In the assumption that the equilibration reactions 1 and 3 are much faster than the decay reaction 4 and with [**4a**] ≫ [**3b**] in our experimental conditions, we obtain the differential equations for the decay of [**3b**] and [**4b**] as follows:

$$-\frac{d[\mathbf{3b}]}{dt} = \frac{2k_4K_3[\mathbf{4b}]^2}{1 + p + 4K_3[\mathbf{4b}]p} \qquad (14)$$

$$-\frac{d[\mathbf{4b}]}{dt} = \frac{2k_4K_3[\mathbf{4b}]^2}{1 + 1/p + 4K_3[\mathbf{4b}]} \qquad (15)$$

$$p = K_1\,[\mathbf{4a}]_0\{[\mathbf{3b}]_0 + [\mathbf{3a}]_0\} + [\mathbf{3a}]_0\{2[\mathbf{3b}] - [\mathbf{3b}]_0\} - \{[\mathbf{3b}]_0 - [\mathbf{3b}]\}^2/\{[\mathbf{3a}]_0 + [\mathbf{3b}]_0 - [\mathbf{3b}]\}^2 \qquad (16)$$

Here $[\mathbf{4a}]_0$, $[\mathbf{3b}]_0$, and $[\mathbf{3a}]_0$ represent the concentrations of the various species immediately after mixing the reactants, i.e. after the very fast equilibration between **3b** and **4a** has taken place but before the much slower decay of dimer **4c** has occurred to any extent.

The experiments for the determination of K_1 were carried out by mixing within an EPR tube a deoxygenated benzene solution of **3b** and of **4a** and starting as soon as possible to record the EPR spectra of the mixture at different times. The concentrations of the reactants were in the range 4 x 10^{-4}–9 x 10^{-4} M for **3b** and 2 x 10^{-3}–8 x 10^{-2} M for **4a**, so that both aroxyl radicals could be observed. The absolute concentrations of species **3b** and **4b** were then determined by integration of the EPR spectra (see Experimental Section) and plotted as function of time as shown in Figure 4. The time dependences of [**3b**] and [**4b**] were then simulated by integrating numerically eqs 14 and 15 using K_1 as the only adjustable parameter.[18] The agreement between the calculated traces and the experimental points, as shown in Figure 4, was very good without any need of introducing some other constant. This may be taken as an indication that other reactions, such as that between galvinoxyl and the 2,6-di-*tert*-butyl-4-methylphenoxyl radical (**4b**) to give a cross dimer, can be completely neglected. The best fitting of the experimental points was obtained with K_1 = (4.03 ± 0.33) x 10^{-2} from which an O—H bond dissociation enthalpy for **4a** of 80.70 ± 0.34 kcal mol^{-1} could be calculated by assuming $\Delta H° \cong \Delta G°$.

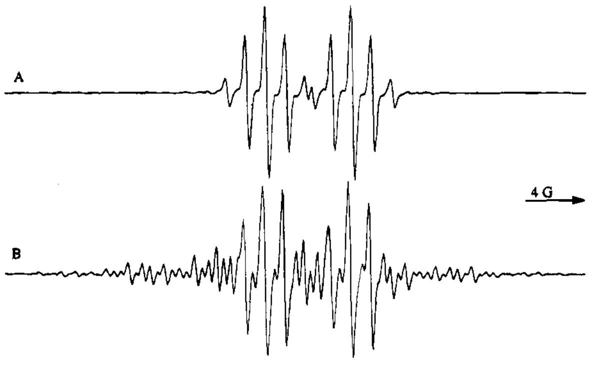
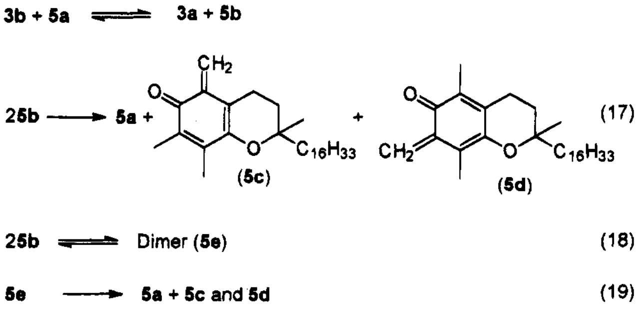


Figure 5. EPR spectra of **3b** (A) and of the mixture **3b** + **5b** (B), in deoxygenated benzene solution.

α-Tocopherol (5a). An attempt to estimate the O—H bond dissociation enthalpy of α-tocopherol (80.4 kcal mol^{-1}) by using kinetic data and a Polanyi-type correlation has been reported by Ingold and co-workers.[19] A value of DH(αT—H) of 76.0 kcal mol^{-1} has been recently obtained from an equilibration study between the aroxyl radicals from α-tocopherol and hindered phenols.[20] The latter determination, however, suffers from the fact that the decay reactions of the equilibrating aroxyl radicals have not been taken into account. In the present investigation we have carried out equilibration studies between galvinoxyl (**3b**) and α-tocopherol (**5a**) by reaction of deoxygenated benzene solutions of these two species in concentrations, i.e. 6 x 10^{-4}–9 x 10^{-4} M for **3b** and 6 x 10^{-4}–1.5 x 10^{-3} for **5a**, appropriate to detect by EPR the simultaneous presence of radicals **3b** and **5b** (see Figure 5). After the reactants were mixed, the intensity of the EPR signals started to decrease with time, as reported in Figure 6, which shows the time evolution of the concentrations of the two radicals determined by numerical double integration of the EPR spectra.

The reaction scheme described by eqs 1 (ArOH = **5a**), 17, 18, and 19 is analogous to that previously discussed for the reaction of **3b** with **4a** and thus K_1 can only be determined if the rate constants for reactions 17 and 19 and the equilibrium constant for reaction 18 are known.



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[18] Values of K_3 and k_4 coincident (within experimental error) with those determined previously were used. The concentrations at zero time of all the reactants can be easily derived once K_1 has been fixed.

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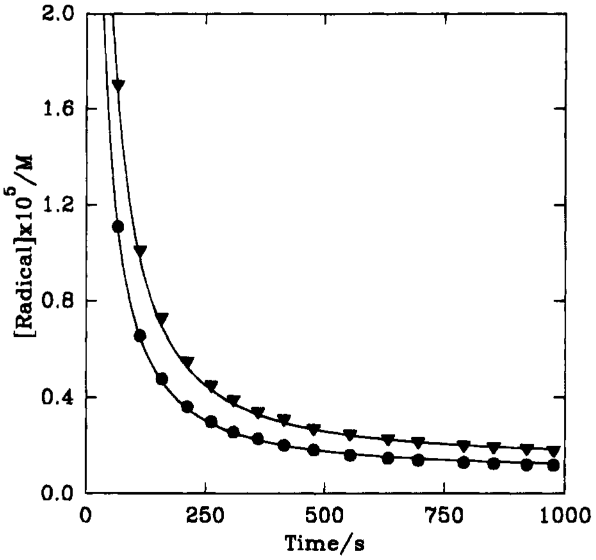

Figure 6. Decay of **3b** (▼) and **5b** (O) generated by mixing **3b** (6.96×10^{-4} M) and **5a** (1.04×10^{-3} M) in benzene.

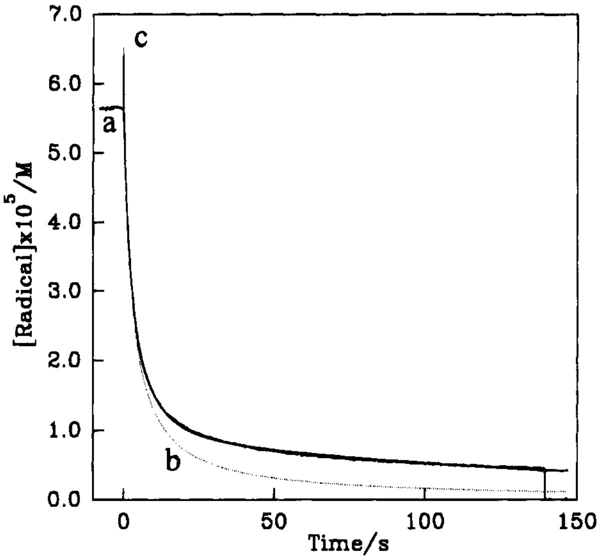

Figure 7. Experimental decay (a) of radical **5b**. Dotted (b) and full (c) lines represent curves simulated adopting second-order kinetics decay or a complete kinetic scheme (eqs 20 and 21).

Several kinetic studies of the decay of the α-tocopheroxyl radical in various solvents can be found in the literature. In all cases bimolecular decay has been observed; however, the reported kinetic constants ($2k_t$) span a very wide range, i.e. 180 $M^{-1}\,s^{-1}$ in $CHCl_3$,[21] 350 $M^{-1}\,s^{-1}$ in cyclohexane,[22] 0.061 $M^{-1}\,s^{-1}$ in benzene,[23] and $3 \times 10^3\,M^{-1}\,s^{-1}$ in benzene.[19] The huge differences between these values have been attributed[19] to the fact that the kinetics of the decay of **5b** may be complicated by the reversible formation of a diamagnetic dimer (eq 18) and of disproportionation products (eq 17). Because of the absence of reliable values for the kinetic constants required for the determination of K_1, we repeated the study of the decay of α-tocopheroxyl radicals. They were generated at room temperature in benzene solution by reaction with *tert*-butoxyl radicals produced by photolysis of $Me_3COOCMe_3$ within the EPR cavity. As shown in Figure 7, the time dependence of the intensity of the EPR signals of **5b** observed when cutting off the light obeyed initially second-order kinetics but then the decay became much slower, reaching almost a plateau. This is indicative of the formation of a dimer of **5b** which behaves as a reservoir of α-tocopheroxyl radicals. By analogy with the case of **4b**, we attempted to analyze these curves by means of eq 11 or 13, but we could not get any proper fitting of the experimental data over a wide range of experimental conditions. We were therefore forced to conclude that the simplified kinetic eqs 11 and 13, which were derived in the assumption that the dimerization reaction is much faster than the decay of either the phenoxyl radical or its dimer, do not describe correctly the time dependence of the disappearance of α-tocopheroxyl radicals.

Table 2. Rate and Equilibrium Constants for the Reactions of α-Tocopherol at 298 K in Benzene Solutions

$2k_{17}$	$(6.03 \pm 2.58) \times 10^3\ M^{-1}\,s^{-1}$
k_{18}	$(1.05 \pm 0.32) \times 10^2\ M^{-1}\,s^{-1}$
k_{-18}	$(2.17 \pm 2.36) \times 10^{-2}\ s^{-1}$
k_{19}	$(1.0 \pm 1.1) \times 10^{-2}\ s^{-1}$
K_{18}	$4.83 \pm 1.83 \times 10^3\ M^{-1}$

Good fitting of the decay traces was instead obtained by numerical integration of the two simultaneous differential equations 20 and 21, where the adjustable

$$\frac{-d[\mathbf{5b}]}{dt} = 2(k_{17} + k_{18})[\mathbf{5b}]^2 - 2k_{-18}[\mathbf{5e}] \qquad (20)$$

$$\frac{d[\mathbf{5e}]}{dt} = k_{18}[\mathbf{5b}]^2 - (k_{-18} + k_{19})[\mathbf{5e}] \qquad (21)$$

parameters were k_{17}, k_{18}, k_{-18}, k_{19} and the concentration of the dimer **5e** at the time where the light is cut off. The rate constants values giving the best agreement with the experimental data are reported in Table 2. With regard to the decay of radical **5b**, this seems to occur essentially by disproportionation rather than by decomposition of the dimer since, in all the examined cases, $k_{17}[\mathbf{5b}]^2$ was found to be much larger than $k_{19}[\mathbf{5e}]$. Additional evidence showing that the decomposition of the dimer is much less important than the disproportionation reaction 17 in determining the decay of **5b** was obtained in the following way. The experimental traces were simulated by considering only one of the two reactions 17 or 19. Good fitting was obtained in both cases; however in the latter one a considerable amount of dimer was predicted to be formed. To check the latter possibility, temperature jump experiments were performed during the decay of the α-tocopheroxyl radical. Since these did not show any appreciable increase in the radical concentration, it is safe to conclude that the dimer is present only to a small amount. On the other hand, this conclusion is also consistent with the results of recent studies.[24,25] It must be however emphasized that although being present at low concentration, the dimer produces appreciable deviations from second-order kinetics in the final part of the decay traces (see Figure 7).

The presence of the dimer **5e** must be taken into account also when examining the reaction between

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[25] α-Tocopheroxyl radicals have been reported to dimerize at low temperature.[26]

galvinoxyl and α-tocopherol. The equilibrium constant for this reaction was determined by analyzing the time dependence of the concentrations of **3b** and **5b** after mixing the reactants (see Figure 6). This was done by numerically integrating the four simultaneous equations (22–25) which fully describe the kinetic behavior of our system in the assumption that reaction 19 can be neglected.

$$\frac{-\mathrm{d}[\mathbf{3b}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathbf{3a}]}{\mathrm{d}t} = k_1[\mathbf{3b}][\mathbf{5a}] - k_{-1}[\mathbf{3a}][\mathbf{5b}] \quad (22)$$

$$\frac{-\mathrm{d}[\mathbf{5a}]}{\mathrm{d}t} = k_1[\mathbf{3b}][\mathbf{5a}] - k_{-1}[\mathbf{3a}][\mathbf{5b}] - k_{17}[\mathbf{5b}]^2 \quad (23)$$

$$\frac{\mathrm{d}[\mathbf{5b}]}{\mathrm{d}t} = k_1[\mathbf{3b}][\mathbf{5a}] - k_{-1}[\mathbf{3a}][\mathbf{5b}] - 2(k_{17} + k_{18})[\mathbf{5b}]^2 + 2k_{-18}[\mathbf{5e}] \quad (24)$$

$$\frac{\mathrm{d}[\mathbf{5e}]}{\mathrm{d}t} = k_{18}[\mathbf{5b}]^2 - k_{-18}[\mathbf{5e}] \quad (25)$$

Here the only unknown parameters were k_1 and k_{-1}; all the other rate constants were allowed to vary around the previously determined values by no more than the experimental error. Due to the experimental conditions employed the first EPR spectrum of the reaction mixture could be recorded ca. 1 min after mixing the reactants. Since at this time equilibration between **3b** and **5a** had already occurred the kinetics was scarcely affected by changes in the absolute values of k_1 and k_{-1}; therefore only their ratio, i.e. the equilibrium constant K_1 (ArOH = **5a**), could be determined as 0.80 ± 0.12. From this value the DH for the O–H bond of α-tocopheroxyl is calculated as 78.93 ± 0.39 kcal mol^{-1}, in the assumption that $\Delta S°$ for reaction 1 (ArOH = **5a**) is negligible.

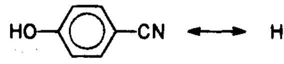
Conclusions

The bond dissociation enthalpies of the OH bond have been determined in a number of phenolic antioxidants by equilibration studies with the stable galvinoxyl radical. With aroxyl radicals decaying at appreciable rates, reliable values of the equilibrium constants were obtained by making measurements of their concentrations at different times after mixing the reactants and by making use, for the analysis of the experimental data, of a kinetic scheme which takes into account all the possible reactions of these radicals. Values of DH(ArO–H) obtained in this way differ by as much as 3 kcal mol^{-1} from those reported in the literature.

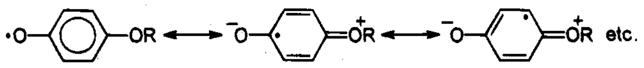
In two cases the equilibrium constants were measured at various temperatures and the corresponding thermodynamic parameters, $\Delta H°$ and $\Delta S°$, determined. Values of the entropy change much smaller than those proposed in a previous investigation[8] were obtained. A semiempirical estimate of $\Delta S°$ for one of these reactions provided a value smaller than 2 cal mol^{-1} K^{-1} which is consistent with those found in the present study. On this basis, the entropic contribution to the free energy change for the equilibration reaction of aroxyl radicals was neglected also in those cases where $\Delta S°$ could no be determined.

All the bond dissociation enthalpies reported here refer to 2,4,6-tri-*tert*-butylphenol, for which a value of 81.24 ± 0.08 kcal mol^{-1}, determined by calorimetry, has been reported.[4] Thus, the absolute values of DH(ArO–H) for phenols **1**–**5** depend on the accuracy of the above measure and may be subject to changes, while the differences between the various DH's can be regarded with confidence.

It is apparent from the data of Table 1 that the bond dissociation enthalpies of the examined phenols increase in the order **1a** < **3a** ≤ **5a** < **4a** ≤ **2a** ≤ **6a**, where the position of probucol (**2a**) is to some extent surprising. Actually, because of the presence of the electron-donating alkylthio substituent in the *para* position, the aroxyl radical from probucol might be expected to be more stabilized than those from the other two phenols (**4a** and **6a**) containing *para* alkyl groups. In fact, DH values in *para*-substituted phenols have been found to depend strongly on the nature of the substituent being linearly correlated with the σ^+ values.[2,3,27,28] This means that electron-withdrawing substituents induce an increase of the bond-dissociation enthalpy, due to the stabilization of the phenol by polar structure such as the one show below for a cyano substituent.



On the other hand, electron-donating groups produce a reduction of DH due to the stabilization of the phenoxyl radical by mesomeric structures bearing a positive charge on the substituent.



It should be however emphasized that the stabilization of phenoxyl radicals by alkoxy or alkylthio groups may only occur when the donating substituent is coplanar with the aromatic ring. This is highly unlikely in probucol due to the bulkiness of the SCMe$_2$SAr group. Actually, in the anion and in the nitroxide radicals from 4-(*tert*-butylthio)nitrobenzene, the dihedral angle formed by the plane of the aromatic ring and the plane defined by the C$_{\text{para}}$, S, and CMe$_3$ atoms, is *ca.* 90°.[29] Since a similar conformation is likely to be adopted by the alkylthio group of probucol, no conjugative stabilization is expected in the aroxyl radical **2b** due to the unfavorable geometry.

As far as α-tocopherol (**5a**) is concerned, the bond-dissociation enthalpy value found in the present work is larger than that of 2,6-di-*tert*-butyl-4-methoxyphenol (**1a**) by 1.32 kcal mol^{-1}. This difference is reduced to 0.86 kcal mol^{-1} at 298 K, if free energy instead of enthalpy variations are considered. Although the lower value of the bond dissociation enthalpy might induce one to consider this phenol a better antioxidant than α-tocopherol, this is not the case since **1a** is disfavored kinetically with respect to **5a** because of the presence of the two bulky *tert*-butyl groups in the *ortho* positions.

Another point worth mentioning is that the α-tocopheroxyl radicals were found to have a remarkably low value of the rate constant for the reversible dimerization,

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i.e. 10^2 M^{-1} s^{-1} at room temperature as compared with 4.5×10^7 M^{-1} s^{-1} for **4b** and 6×10^7 M^{-1} s^{-1} for the 2,6-di-*tert*-butylphenoxyl radical.[16] This reluctance to dimerize is presumably due to the fact that all the ring carbons are substituted and therefore reflects the steric hindrance to the approach of two aroxyl radicals to form the dimer. An important consequence of this slow rate of dimerization is that α-tocopheroxyl radicals that are formed at very low concentrations in systems where vitamin E exerts its antioxidant action will have lifetimes long enough to effectively trap a second peroxyl radical.

Experimental Section

Materials. *Di-tert*-butyl peroxide (Fluka) was passed through alumina before use to remove *tert*-butyl hydroperoxide which in principle may react with the phenoxyl radical.[30] All other chemicals were commercially available and used as received. The purity of α-tocopherol was monitored by measuring the absorbance at 292 nm (ϵ = 3260 M^{-1} cm^{-1}) in ethanol by UV spectroscopy.

EPR Spectra. EPR spectra were recorded on a Bruker ESP 300 spectrometer equipped with a Hewlett-Packard 5350B frequency counter for the determination of the g-factors which were corrected with respect to that of the perylene radical cation (2.00258). Photolysis was carried out with the light from a 500-W high pressure mercury lamp filtered with an AEO interference filter (maximum transmittance 366.3 nm). The temperature was controlled with a standard variable temperature accessory and was monitored before and after each run with a copper–constantan thermocouple. Radical concentrations were measured by comparing the double integral of the EPR spectrum of the phenoxyl radicals with that given by a DPPH solution of known concentration and by using an artificial ruby crystal as internal standard.

EPR spectral parameters of phenoxyl radicals; 1b, $a_H(2H_{meta})$ = 0.93 G, $a_H(OCH_3)$ = 1.53 G, g = 2.0047_3; **2b** $a_H(2H_{meta})$ = 1.39 G, g = 2.0055_4; **3b** $a_H(4H_{meta})$ = 1.38 G, $a_H(CH)$ = 5.97 G, g = 2.0045_0; **4b** $a_H(2H_{meta})$ = 1.67 G, $a_H(p\text{-}CH_3)$ = 11.20 G, g=2.0046_2; **5b** $a_H(C(4)H_2)$ = 1.60 G, $a_H(C(5)H_3)$ = 6.10 G, $a_H(C(7)H_3)$ = 4.65 G, $a_H(C(8)H_3)$ = 1.02 G, g = 2.0047_7; **6b** $a_H(2H_{meta})$ = 1.71 G, $a_H(p\text{-}CCH_3)$ = 0.38 G, g = 2.0046_4.

Kinetics of the Decay of Aroxyl Radicals. Aroxyl radicals were generated by a flash of intense UV irradiation of a sample containing ca. 2×10^{-2} M of the appropriate phenol in benzene/di-*tert*-butyl peroxide (10:1 (v/v)). These solutions were degassed and sealed under vacuum. The decay of the aroxyl radical was monitored at a fixed magnetic field corresponding to the main peak in the EPR spectrum. Digitized decays were transferred to an AT-486 (33 MHz) personal computer in order to analyze the traces. Integration of the simultaneous differential equations was performed by means of the Runge–Kutta–Fehlberg method which allows the optimization of the integration step.[31] In order to evaluate kinetic parameters an iterative least-squares fitting procedure based on a systematic application of Monte Carlo methods was performed.[32] The parameters are varied by small but random amounts and the new set is retained if a better fit is obtained.

Equilibrium Constants. A weighed amount of phenol was placed in the side arm of an EPR tube and a solution of known concentration of galvinoxyl was placed in the main tube. The oxygen was removed from the solution by freeze–pump cycles and the tube was sealed under nitrogen. Before mixing the reactants, the EPR spectrum of galvinoxyl was recorded. For phenols **4a** and **5a** the EPR spectra were recorded as soon as possible after mixing (ca. 1 min) and the signal was followed at different times by using a low conversion time (20.5 ms). The total amount of radical was measured by comparing the double integral of the EPR spectrum of both radicals with that given by a DPPH solution of known concentration and by using an artificial ruby crystal as internal standard. When no overlap was observed with the lines of the other radical, the concentration ratio between the phenoxyl and galvinoxyl radicals was determined by comparing the intensity of the lines of the galvinoxyl spectrum before and after mixing. For accuracy the line width was measured by numerical correlation of the experimental line with a simulated Gaussian derivative line.[33] When line overlapping was observed the ratio of the two radicals was determined by comparison with computer-simulated spectra.

Acknowledgment. Financial support from MURST and from CNR (Rome) is gratefully aknowledged.

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