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Electronic and Hydrogen Bonding Effects on the Chain-Breaking Activity of Sulfur-Containing Phenolic Antioxidants

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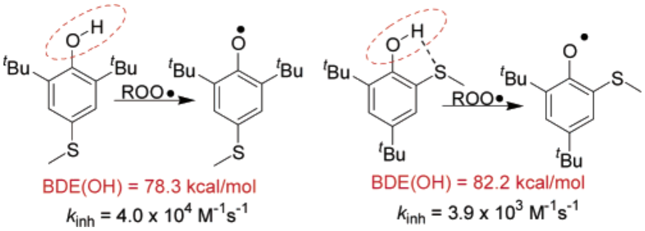

A kinetic and thermodynamic investigation of phenols *para*-substituted with thiyl (SR), sulfinyl (SOR), and sulfonyl (SO_2R) groups and *ortho*-substituted with thiyl groups is reported. The effect of the sulfur substituents on the O−H bond dissociation enthalpy values, BDE(O−H), was measured by means of the EPR radical equilibration technique and the reactivity toward peroxyl radicals, k_{inh}, of these phenolic antioxidants was determined by inhibited autoxidation studies. An inverse correlation between these two parameters was found. A *p*-SMe substituent decreased the BDE(O−H) value to a lesser extent than a *p*-OMe group (−3.6 vs −4.4 kcal/mol), whereas the effect of the same groups in an *ortho* position showed an opposite trend (−0.85 vs −0.2 kcal/mol). The latter result is explained in terms of the different strength of the intramolecular hydrogen bond between the OH proton and the sulfur or oxygen substituents in *ortho* derivatives. ESI-MS analysis of the products formed by reacting the sulfides with peroxyl radicals from the azoinitiator AIBN revealed the formation of a complex mixture of products, which may play an important role in determining the overall antioxidant activity of the parent compounds.

Introduction

Among inhibitors of free radical oxidation of hydrocarbon substrates, sulfur-containing phenols are of particular interest since they can behave both as chain-breaking antioxidants by scavenging peroxyl radicals through hydrogen atom transfer from the phenol group (eq 1) and as preventive antioxidants by decomposing hydroperoxides to the corresponding alcohols by a reaction involving nucleophilic attack by sulfur on oxygen.[1] Moreover, since sulfur is considered to be more effective than oxygen at stabilizing a neighboring radical center,[2] these compounds might be better antioxidants than the analogue phenols containing oxygen substituents.

$$ROO^\bullet + ArOH \xrightarrow{k_{inh}} ROOH + ArO^\bullet \qquad (1)$$

$$ROO^\bullet + ArO^\bullet \rightarrow \text{products} \qquad (2)$$

A series of derivatives related to 1-thio-α-tocopherol were investigated in the late 1980s by Ingold and co-workers and, contrary to expectations, were less reactive toward peroxyl radicals than the corresponding chromane derivatives.[3] In particular, the lower reactivity was found to be due both to the smaller k_{inh} (see eq 1) and to the fact that they trap fewer than two peroxyl radicals per molecule. This also indicates that the

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mechanism of inhibition is somewhat different from that one simply consisting in the two reactions 1 and 2. On the other hand, an investigation of 2,3-dihydrobenzo[*b*]furan-5-ol and 2,3-dihydrobenzo[*b*]thiophene-5-ol, i.e., analogues of tocopherol having a five-member condensed ring, suggested that the antioxidant capacity of the sulfur derivative is better than that of the oxygenated one.[4]

In a comparative study of the antioxidant properties of cyclic aromatic amines,[5] sulfur-containing derivatives are less reactive than the corresponding oxygenated ones. Actually, substitution of the heterocyclic oxygen atom of phenoxazine with sulfur (phenothiazine) or selenium (phenoselenazine) increased the dissociation enthalpy (BDE) of the N−H bond by 2.1 and 3.2 kcal/mol, respectively, thus making the hydrogen atom transfer from the latter two amines to an attacking radical less exoergonic. Accordingly, the rate constants for the reaction with both $ROO^{\bullet}$ and $CH_3^{\bullet}$ radicals decreased in the order O > S > Se.

In recent studies on the antioxidant effect of bis(4-hydroxy-3,5-di-*tert*-butylphenyl) sulfides and polysulfides,[6] it has been reported that these compounds retard the hydrocarbon oxidation both by terminating the oxidation chains by hydrogen transfer to peroxyl radicals and by catalyzing the decomposition of hydroperoxides. The inhibiting activity was found to increase with the number of sulfur atoms. A similar investigation on related sulfides also reached the conclusion that these considerably surpass the antioxidative ability of the commercial 2,6-di-*tert*-butyl-4-methylphenol (BHT).[7]

4-Thiaflavan derivatives, obtained by introducing a sulfur atom on the C ring of flavan, have been synthesized and their antioxidant activity evaluated.[8] These heterocyclic sulfides showed antioxidant properties similarly to the parent flavans, while their oxidation to the corresponding sulfoxides gave rise to an almost complete loss of activity.

To better clarify the behavior of sulfur derivatives and to estimate on a quantitative basis the effect of sulfur substituents on the antioxidant properties of phenols, we have undertaken a thermodynamic and kinetic study of 2,6-di-*tert*-butylphenols substituted at the 4 position with thiyl (SR), sulfinyl (SOR), and sulfonyl (SO_2R) groups. The last ones were investigated because sulfides are easily oxidized to give sulfoxides or sulfones under the experimental conditions employed to carry out autoxidation studies. Therefore, the structure of the oxidation inhibitor may change during the course of the reaction with a consequent change in the antioxidant behavior.

We have also investigated a couple of phenols containing thiyl substituents *ortho* to the hydroxyl group because these structures are present in the active site of galactose oxidase,[9] where the tyrosyl radical is connected to a neighboring cysteine through a thioether bond.[10] Knowledge of the thermodynamic and kinetic behavior of such modified amino acid and of the effect of sulfur on the stability of *o*-phenoxyl radical centers is essential to develop new artificial enzymes for the green oxidation of alcohols.[11]

SCHEME 1

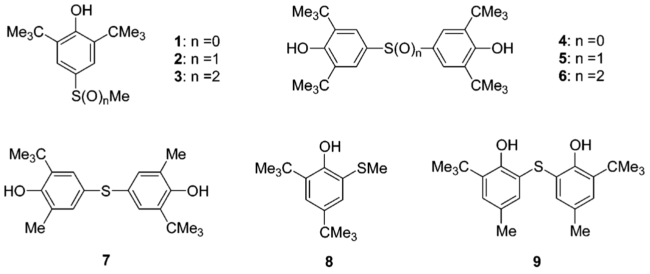

TABLE 1. EPR Spectral Parameters for Phenoxyl Radicals from Substituted Phenols Measured at Room Temperature in Benzene Solution; Hyperfine Splitting Constants in gauss (1 G = 0.1 mT)

phenol	$a(2H_m)$	$a(3H_{Me})$	a(other)	g-factor
1	1.30	2.24		2.0055
3	2.19	1.56		2.0048
4	1.32			2.0054
6	2.12			2.0048
7	1.22, 1.38[a]	5.53		2.0054
8	1.29, 1.59	1.89	0.34 ($9H_{t-But}$)	2.0053
9	1.13, 1.84	10.17		2.0050

[a] From computer simulation.

Results

The investigated phenols are shown in Scheme 1. These structures were chosen in order to study the effect of sulfur substituents in the ring positions conjugated with the hydroxyl group. *Ortho tert*-butyl groups are helpful, when performing EPR studies, for increasing the persistency of the corresponding phenoxyl radicals due to the sterical protection of the radical oxygen center.

EPR Spectra. The phenoxyl radicals from the examined compounds were produced at room temperature inside the cavity of an EPR spectrometer by reacting the phenols with alkoxyl radicals generated photolytically from di-*tert*-butyl peroxide in deoxygenated benzene solutions:

$$ArOH + RO^{\bullet} \rightarrow ROH + ArO^{\bullet} \qquad (3)$$

Highly persistent radicals showing easily interpretable EPR spectra were always obtained with sulfides and sulfones; their spectral parameters (hyperfine splitting constants and *g*-factors) shown in Table 1 are consistent with those previously reported for similar radicals.[12] On the other hand, the sulfoxides **2** and **5**, under the same experimental conditions, afforded only weak EPR signals due to transient paramagnetic species. This is not unexpected, since it has been reported by Gilbert et al. that irradiation of 4-sulfinyl phenols, either in the presence or in the absence of di-*tert*-butyl peroxide, affords sulfinyl radicals formed by cleavage of the S(O)−R bond.[12]

From the data of Table 1 it appears that the *meta* splittings in the phenoxyl radicals from sulfides **1** and **4** (ca 1.30 G) are

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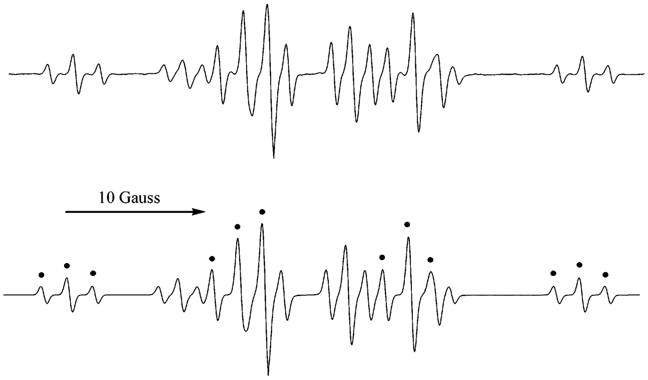

FIGURE 1. Experimental (upper) and simulated room-temperature EPR spectrum obtained by photolyzing a mixture of BHT (0.055 M) and **7** (0.19 M) in deoxygenated benzene containing 10% di-*tert*-butyl peroxide. The 12 lines of the phenoxyl radical from BHT are marked with a dot.

lower than those measured ($a(2H_m) = 1.95G$)[13] in the corresponding radical without 4-substituents (i.e., that obtained from 2,6-di-*tert*-butylphenol), whereas in the radicals from sulfones **3** and **6** the coupling at the meta hydrogens (ca 2.15 G) is larger. This behavior is peculiar of electron donor and electron acceptor substituents, respectively.[14] Since also the *g*-factors of the radicals from sulfides and sulfones differ considerably, being larger for the former ones, there is little doubt that the observed species result from the abstraction of the hydroxyl hydrogen atom of the investigated phenols.

O−H Bond Dissociation Enthalpies (BDE). The O−H BDE values for the title compounds were determined by using the EPR radical equilibration technique that, among the various experimental methods used for the determination of bond strengths, seems to guarantee at present the best accuracy.[13,14] To this purpose we measured the equilibrium constant, K_e, for the hydrogen atom transfer reaction between a reference phenol (Ar′OH) and one of the examined phenols (ArOH) and the corresponding phenoxyl radicals (eq 4) generated under continuous photolysis at room temperature (25 °C) in deoxygenated benzene solutions containing 10% of di-*tert*-butyl peroxide.

$$\mathrm{ArOH} + \mathrm{Ar'O}^{\bullet} \rightleftharpoons \mathrm{ArO}^{\bullet} + \mathrm{Ar'OH} \qquad (4)$$

2,6-Di-*tert*-butyl-4-methylphenol (BHT), whose revised BDE value is 80.1 kcal/mol,[15] was always used as reference phenol, except in the case of **8**, which was equilibrated with 2,4,6-trimethylphenol (BDE = 82.2 kcal/mol). As an example of the quality of the EPR spectra obtained, Figure 1 shows that one of the mixture of **7** and BHT.

Measurements were repeated under different light intensity in order to check the constancy of K_e and, therefore, the achievement of the equilibrium. In the calculation of K_e, the initial concentration of ArOH and Ar′OH were used, and the relative radical concentrations were obtained both by numerical integration and by simulation of the EPR spectra. The BDEs for the species ArOH were calculated, in the assumption that the entropic term can be neglected,[13] by means of eq 5 from K_e and the BDE value of the reference phenol Ar′OH.

$$\mathrm{BDE(ArO\text{-}H)} \cong \mathrm{BDE(Ar'O\text{-}H)} - RT\ln(K_e) \qquad (5)$$

Rate Constants of Inhibition. The determination of the rate constant for the reaction with peroxyl radicals, k_{inh} (eq 10), of the above derivatives was made by studying the inhibition of the thermally initiated autoxidation of either cumene or styrene. Cumene was preferentially used with weak inhibitors, because its lower oxidizability with respect to styrene allows a better detection of the induction period.

$$\mathrm{initiator} \xrightarrow{R_i} \mathrm{R}^{\bullet} \qquad (6)$$

$$\mathrm{R}^{\bullet} + \mathrm{O_2} \rightarrow \mathrm{ROO}^{\bullet} \qquad (7)$$

$$\mathrm{ROO}^{\bullet} + \mathrm{RH} \xrightarrow{k_p} \mathrm{ROOH} + \mathrm{R}^{\bullet} \qquad (8)$$

$$\mathrm{ROO}^{\bullet} + \mathrm{ROO}^{\bullet} \xrightarrow{2k_t} \mathrm{products} \qquad (9)$$

$$\mathrm{ROO}^{\bullet} + \mathrm{ArOH} \xrightarrow{k_{inh}} \mathrm{ROOH} + \mathrm{ArO}^{\bullet} \qquad (10)$$

$$\mathrm{ROO}^{\bullet} + \mathrm{ArO}^{\bullet} \rightarrow \mathrm{products} \qquad (11)$$

The reaction was followed by monitoring the oxygen consumption during the autoxidation with an automatic recording gas absorption apparatus described previously,[19] which uses as detector a commercial differential pressure transducer. The reactions, initiated by the thermal decomposition of AMVN (2,2′-azobis(2,4-dimethyl-valeronitrile)), were carried out at 30 °C under controlled conditions in air-saturated solution of the oxidizable substrate, both in the absence and in the presence of each antioxidant. α-Tocopherol was used as reference chain-breaking inhibitor.

The inhibition rate constants k_{inh} of each compound were determined by means of a kinetic treatment[20] consisting in the measure of the oxidation rate in the presence ($-d[O_2]/dt = R$) and in the absence ($(-d[O_2]/dt)_0 = R_0$) of antioxidant as a function of time. The k_{inh} values were obtained from the slope of the function F (eq 12) against time using the known rate constants for the propagation reaction, k_p (eq 8), of the oxidizable substrates (RH).

$$F = \ln\frac{1 + R/R_0}{1 - R/R_0} - \frac{R_0}{R} = \frac{k_{inh}R_0}{k_p[\mathrm{RH}]}\,t + \mathrm{constant} \qquad (12)$$

In the case of styrene, k_p is 41 M^{-1} s^{-1}.[21] In the case of cumene, its oxidation kinetics being dependent on substrate

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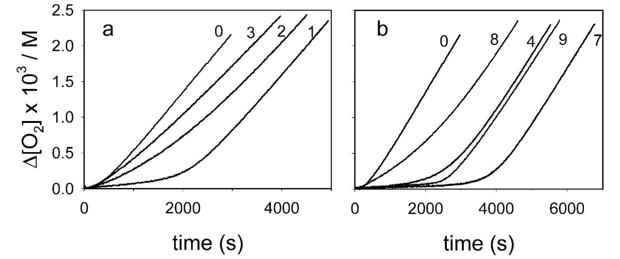

FIGURE 2. Oxygen consumption observed at 30 °C during the AMVN (5×10^{-3} M) initiated autoxidation of cumene (7.1 M) in the absence (0) and in the presence of some sulfur-containing phenols (5.0×10^{-6} M).

TABLE 2. O-H Bond Dissociation Enthalpies (BDE) of Substituted Phenols 1−9 Measured at Room Temperature in Benzene Containing 10% Di-*tert*-butyl Peroxide, Rate Constants k_{inh} for Their Reaction with Peroxyl Radicals in Cumene (or Styrene) at 30 °C, and Number of Radicals Trapped by Each Antioxidant Molecule (*n*)[g]

compd	BDE/kcal mol^{-1}	oxidizable substrate[a]	$k_{inh} \times 10^{-4}$/M^{-1} s^{-1}	*n*
1	78.3 ± 0.1	C	3.0 ± 0.2	1.7 ± 0.1
		S	4.0 ± 0.3	
2	81.6[b]	C	0.29 ± 0.05	1.6 ± 0.2
3	81.7 ± 0.4	C	0.22 ± 0.01	1.3 ± 0.4
4	78.5 ± 0.2	C	2.7 ± 0.1	1.7 ± 0.1
5		C	0.34 ± 0.04	2.2 ± 0.1
6	82.3 ± 0.3	C	0.13 ± 0.02	1.6 ± 0.1
7	79.6 ± 0.2	S	61 ± 10	3.1 ± 1
8	82.2 ± 0.2	C	0.39 ± 0.05	1.6 ± 0.2
9	81.0 ± 0.1	S	21 ± 1	2.2 ± 0.1
BHT	80.1 ± 0.1[c]	S	1.1[d]	2
BHA[e]	77.4 ± 0.1[c]	S	11.0[f]	2

[a] Measured in cumene (C) or in styrene (S). [b] Estimated from the plot of Figure 5 by using the experimentally determined values of k_{inh}. [c] Revised value, ref 13,15. [d] From ref 22. [e] 2,6-di-*tert*-butyl-4-methoxyphenol. [f] From ref 18. [g] Reported data are the mean of three or more determinations with the corresponding standard errors.

concentration,[21] the k_p constant was calculated as 0.32 M^{-1} s^{-1} from our previously reported $2k_t$ value of 4.6×10^4 M^{-1} s^{-1}, measured by following the decay of the cumylperoxyl radicals in neat cumene by EPR,[22] and the oxidizability of neat cumene ($k_p/2k_t^{0.5} = 1.5 \times 10^{-3}$ M$^{-0.5}$ s$^{-0.5}$).[21]

The term *n* (eq 13) represents the stoichiometric coefficient, i.e., the number of peroxyl radicals trapped by each antioxidant molecule, and is determined from the length of the induction period τ during which the rate of the oxygen consumption is strongly reduced (see Figure 2). The values of τ were obtained by following the procedure suggested in ref 20 and described in details in the Experimental Section. The results of these determinations are reported in Table 2.

$$n = \frac{R_i \tau}{[\mathrm{ArOH}]} \qquad (13)$$

Figure 2 shows that the three sulfur derivatives **1**−**3** behave as inhibitors of the initiated autoxidation of cumene, their antioxidant activity decreasing with increasing degree of oxidation of sulfur, being larger for the sulfide and very poor for the sulfone. When using the bis-phenols **4**, **5**, and **6** as inhibitors, oxygen uptake traces surprisingly similar to those obtained with **1**, **2**, and **3** at the same concentration, respectively, were observed. This was unexpected since d[O$_2$]/d*t* values twice as small and stoichiometric coefficients twice as large as those of the monophenols **1**−**3** were predictable in the bisphenols as a result of the presence of two hydroxyl groups, as found with 4,4′-methylenebis(2,6-di-*tert*-butylphenol).[23] It should, however be emphasized that a similar result ($n = 2$) was reported by Farzaliev et al. when inhibiting with **4** the AIBN initiated autoxidation of cumene at 60 °C.[6]

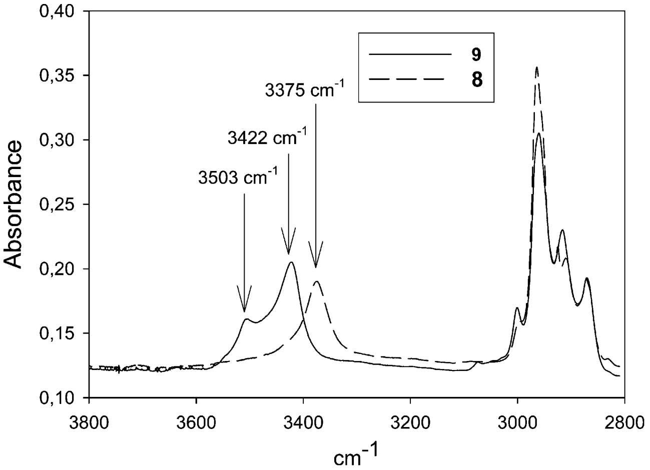

FIGURE 3. FT-IR spectra of 0.05 M of **8** (dashed line) and **9** (continuous line) in CCl$_4$ solution.

An anomalous behavior was also shown by bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl)sulfide (**7**), which differs from **4** for bearing a methyl rather than a *tert*-butyl substituent at one of the ring positions *ortho* to the hydroxyl group. Actually, **7** (see Figure 2) terminates 3 radical chains instead of the 4 expected for bis-phenols. A discussion about the possible reasons of these differences is reported later in this paper.

The antioxidant activity has also been studied for phenol **8** and bis-phenol **9** containing a divalent sulfur atom *ortho* to the hydroxyl groups. The oxygen uptake traces recorded during the inhibited oxidation of cumene, shown in Figure 2, clearly indicate that the bis-phenol **9** is by far a much better oxidation inhibitor than **8**. The ratio of the inhibition rate constants, experimentally determined as described above, is ca. 54 in favor of **9**. Also in this case, as with **4**, the number of oxidation chains *n* terminated by each molecule of inhibitor is about 2 despite the presence of two phenolic units in the molecule.

FT-IR Measurements. In the two compounds **8** and **9**, containing *ortho* sulfur substituents, intramolecular hydrogen bonding between the hydroxyl proton and the sulfur atom may take place, as revealed by previous IR[24] and NMR[25] studies on related derivatives. Since this interaction has a strong effect on the antioxidant properties of phenols,[23,26] we carried out FT-infrared measurements in order to confirm these reports and to identify the nature of the hydrogen bonded species.

Figure 3 shows the FT-IR spectra of both phenols (0.05 M) recorded at room temperature in carbon tetrachloride, in the

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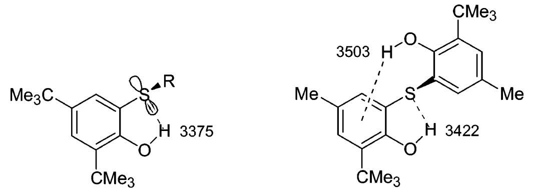
SCHEME 2



2800−3800 cm^{-1} range. The spectrum of the mono-phenol **8** shows a single peak in the O−H absorption region, centered at a frequency (3375 cm^{-1}) characteristic of an intramolecularly hydrogen bonded species. Since the absence of lines above 3600 cm^{-1} indicates that no free hydroxyl group is present, **8** must exist in a single geometry presumably similar to that adopted by 2-(methylthio)phenol, for which IR[24] and NMR[25] evidence suggests that the preferred conformation is that one where the OH···S interaction forces the 3p orbital on sulfur into the benzene plane and the methyl group completely out of the molecular plane (see Scheme 2).

The IR spectrum of the bis-phenol **9** shows, instead, two absorptions: one centered at 3422 cm^{-1} and the other at 3503 cm^{-1}. Both positions and intensities of these two bands are independent of the phenol concentration and their frequencies are characteristic of intramolecularly hydrogen bonded hydroxyl groups. The former one, observed at a frequency close to that one of the only band detected in **8**, can be attributed to the OH group H-bonded to the sulfur atom,[25] whereas the latter absorption (observed at a higher frequency and thus indicative of a weaker H-bonding interaction) should be due to the second hydroxyl group H-bonded either to the π-electrons of the benzene ring or to other OH group. A possible structure for **9** is depicted in Scheme 2.

Product Studies. To clarify the reason for the anomalous n values of compounds **4**, **7**, and **9**, products formed when reacting sulfides **1**, **4**, **7**, **8**, and **9** with peroxyl radicals were studied by electrospray ionization mass spectrometry (ESI-MS),[27] a technique that has been proven to give useful information about intermediates occurring during the autoxidation reactions.[23,26] An acetonitrile (ACN) solution of these sulfides (1×10^{-3} M), containing a large excess of azo-bisisobutyronitrile (AIBN, 5×10^{-2} M), was kept at 60 °C in an open atmosphere for 1 h, and the crude reaction mixture, diluted with methanol, was injected in the spectrometer.

The results obtained using the negative ion detection mode, reported in Figure 4, show that after 15−30 min, in addition to the peak of the deprotonated parent phenol $[M - 1]^-$, two peaks with mass $[M - 1 + 16]^-$ and $[M - 1 + 32]^-$ are present, this indicating that the starting phenol incorporated one and two oxygen atoms, i.e., that it was oxidized to the corresponding sulfoxide and sulfone, respectively. Only in the case of bis-phenols **4**, **7**, and **9**, a strong peak at m/z values lower than that of the parent phenol was also present (m/z = 285, 243, and 243, respectively), corresponding to the mass of a cleavage product in which the sulfur atom is further oxidized to sulfate (R-SO$_3$H). In the case of **7** a strong peak at m/z = 242 was also observed, for which we have no reasonable explanation.

Using the positive ion detection mode, very complex spectra were obtained (not shown), probably because of the tendency of sulfur-containing molecules to give unstable radical cations under electrospray conditions.[28] Nevertheless, weak peaks derived from the addition of peroxyl radicals from AIBN ((CH$_3$)$_2$CNCOO$^\bullet$; MW = 100) on the phenoxyl radicals obtained by hydrogen abstraction from the parent phenols were observed as ^{23}Na complexes, together with signals at +16 m/z and at +32 m/z.

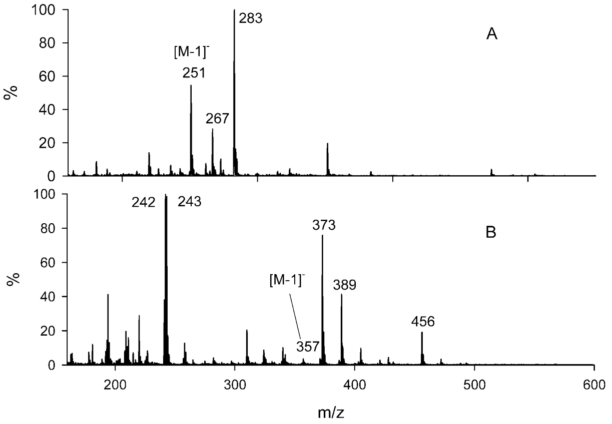


FIGURE 4. Negative ion mode ESI-MS spectra of the products formed by reacting AIBN (5×10^{-2} M) in ACN under air at 60°, with the substituted phenols **1** (**A**, sample reacted for 15 min) and **7** (**B**, sample reacted for 30 min).

Since sulfur-containing molecules are known to decompose hydroperoxides via a nonradical mechanism,[20] the peaks with mass +16 and +32, observed using both the negative and the positive ion mode, might derive from the reaction between antioxidant and the hydroperoxides formed during the autoxidation. To check this possibility, phenol **7** (1×10^{-3} M) was incubated for 1 h at 60 °C in ACN with an amount of cumene hydroperoxide similar to that produced during the first period of the autoxidation reaction (1×10^{-3} M). Under these conditions, no peaks derived from the oxidation of **7** to sulfoxide or sulfone were observed, in line with the low rate constants reported for such reactions.[20]

Discussion

Electronic Effect. The relative efficiency as oxidation inhibitors of the investigated sulfides, sulfoxides, and sulfones **1**−**6** is in agreement with the well-known effect that *para* substituents have on the BDE values of phenols, i.e., strong O−H bonds are brought about by electron acceptors (SOR and SO$_2$R) and weak bonds by electron donors (SR).[14] The additive contribution of the *p*-thiomethyl group, obtained by subtracting to the measured BDE(O−H) values of **1** the BDE(O−H) of phenol (86.7 kcal/mol)[15] and the known contribution of two *o*-*tert*-butyl groups (−4.8 kcal/mol),[14] is −3.6 kcal/mol, a value between methyl (−1.7 kcal/mol) and methoxyl (−4.4 kcal/mol) groups.[14] This result shows that the sulfur atom induces a smaller (O−H) bond strength than oxygen, similarly to what found in phenothiazines for the N−H bond strength.[5] It is somewhat surprising that the BDE values of sulfones **3** (81.7 kcal/mol) and **6** (82.3 kcal/mol) are very close to that of 2,6-di-*tert*-butylphenol (81.9 kcal/mol),[13] this implying that a *p*-SO$_2$R group, which is considered a strong electron-withdrawing substituent, behaves similarly to a *para* hydrogen atom. This does not seem to be due to some experimental artifact since

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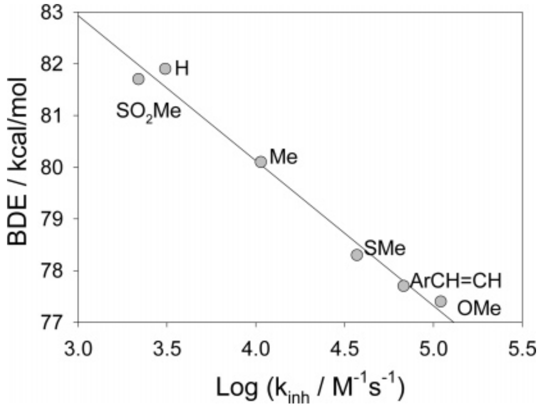

FIGURE 5. Bond dissociation enthalpies (BDE) of 4-substituted 2,6-di-*tert*-butylphenols against the logarithm of the rate constant for their reaction with peroxyl radicals. For experimental data see the present paper and ref 31.

even the inhibition rate constants k_{inh} for **3** and **6** (2.2 and 1.3 $\times$ 10^3 M^{-1} s^{-1}, respectively) are comparable to that of 2,6-di-*tert*-butylphenol (3.1 $\times$ 10^3 M^{-1} s^{-1}).[18] This point deserves more attention and seems worth to be further investigated by a computational approach.

Under the present experimental conditions, no EPR spectra of the phenoxyl radicals from the two sulfoxides **2** and **5** were observed, and thus the corresponding O−H bond dissociation enthalpies could not be measured. It was, however, possible to estimate these values from the inhibition rate constant k_{inh}. In fact, it is known that BDEs vary linearly with the logarithm of k_{inh} for phenols having the same *ortho* substituents. Figure 5 shows the plot obtained by using all the reported BDE and k_{inh} literature data for 4-substituted 2,6-di-*tert*-butylphenols. From this plot the BDE value of the sulfinyl derivative **2** can be estimated as 81.6 kcal/mol.

The O−H BDEs of the sulfides **1** and **4**, when compared to that reported previously for probucol (2,2-di(4-hydroxy-3,5-di-*tert*-butylphenylthio)propane) 81.1 kcal/mol,[29,15] are lower by ca. 1.8 kcal/mol despite the structural similarity of these compounds. It should, however, be pointed out that the alkylthio substituent *para* to the OH group of probucol, i.e., $SC(Me)_2SAr$, is much bulkier than those of both **1** and **4**. Thus, it is conceivable that the geometry adopted by the alkylthio group in probucol and in the corresponding phenoxyl radical is out of the aromatic plane, whereas in **1** (and presumably in **4**) the SR group lies on the molecular plane.[12] Since in organic free radicals the electronic character of alkylthio substituents conjugated with the radical center changes with conformation,[30] it seems reasonable to explain the larger BDE value determined in probucol, with respect to **1** and **4**, in terms of the different geometry adopted by these phenols and the corresponding phenoxyl radicals.

Hydrogen Bond Effects. The additive contribution of an *o*-SCH_3 group to the phenolic BDE(O−H) can be determined as −0.85 kcal/mol, by subtracting the contribution of phenol and of two *tert*-butyl groups (*o*-CMe_3 = −1.75; *p*-CMe_3 = −1.9 kcal/mol)[14] to the experimental BDE(O−H) value of **8**. This value is significantly smaller than the contribution of a *p*-SCH_3 group (−3.6 kcal/mol) because of the formation of an intramolecular hydrogen bond in the parent phenol. Actually, the IR spectrum of Figure 3 shows a single peak (at 3375 cm^{-1}) in the region above 3000 cm^{-1}, indicating that the structure adopted in solution at room temperature is that one where the OH is pointing toward the SCH_3 group.

TABLE 3. Additive Group Effect on the Phenolic BDE(OH) of Thiomethyl and Methoxyl Substituents

	ΔBDE(O−H) (kcal/mol)	
	SCH_3	OCH_3
ortho	−0.85	−0.2
para	−3.6	−4.4

It may be interesting to compare these numbers with the corresponding ones reported for the methoxyl group (see Table 3) in *ortho* and *para* positions, i.e., −0.2 and −4.4.[14] This suggests that the intramolecular hydrogen bond of the phenolic OH proton to the adjacent SMe group is weaker than that to an OMe group.

A point worth of discussion is also the large difference between the values of k_{inh} and BDE of sulfides **8** and **9**, both having a thio substituent *ortho* to the hydroxyl group. Actually, the bisphenol **9** is 54 times more reactive than **8**, instead of being only twice more reactive as expected from statistics. This difference can be rationalized on the basis of the structure of the two antioxidants as discussed above. In the intramolecularly hydrogen bonded *o*-methylthio phenol **8**, the bridge between the hydroxyl hydrogen and the adjacent sulfur atom (Scheme 2) increases the O−H bond dissociation enthalpy by stabilizing the starting phenol and makes more difficult for steric reasons the approach of peroxyl radicals to the OH group. The result is a low reactivity toward attacking radicals for both thermodynamic and kinetic reasons. In the bisphenol **9** instead, the OH group intramolecularly hydrogen bonded to sulfur should be scarcely reactive as in **8**, whereas the second one, giving a weaker H-bond (presumably to the π-electrons of the other benzene ring) is less embedded in the bulk of the molecule and therefore more easily accessible to peroxyl radical. Thus, the hydrogen atom of the second OH group can be abstracted more easily because it is less sterically hindered and is characterized by a lower bond strength (the BDE value is smaller by 1.2 kcal/mol than that of **8**).

Mechanism of Inhibition. In the case of sulfide **1**, the shape of the oxygen uptake trace and the measured induction period seems to indicate that it behaves as a classical chain-breaking phenol antioxidant capable of trapping ca. two peroxyl radicals for each antioxidant molecule. This implies that the phenoxyl radical formed in the first stage of the inhibition reaction reacts with peroxyl radicals to give a quinolide peroxide similarly to alkyl-substituted phenols such as BHT.[1,20] From the ESI-MS spectra of the reaction mixture of **1** with AIBN this adduct can be identified as the Na^+ complex by positive ion detection mode at m/z = 374. In the negative ion detection mode (see Figure 4A), besides the starting sulfides, peaks due to the corresponding sulfoxide and sulfone were also observed. Since no oxidation products could be detected by ESI-MS when reacting **1** with cumene hydroperoxide, this means that the formation of sulfoxides and sulfones is due to the reaction of the sulfide with peroxyl radicals and not with peroxides.

In the case of bisphenol **4**, the length of the induction period is one-half of the expected value since only two peroxyl radicals per molecule are trapped, despite the presence of two phenolic

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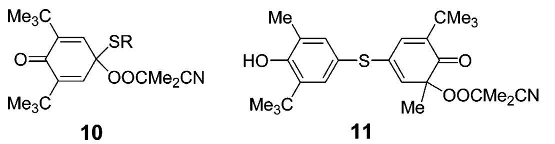
SCHEME 3



10 **11**

moieties. The same result was previously found by other authors who performed similar measurements in cumene at different temperatures.[6] The presence in the ESI-MS spectra of the products of reaction between **4** and AIBN of an intense peak at $m/z = 285$ (not shown) corresponding to a cleavage product in which sulfur is oxidized to sulfate seems to suggest that, after trapping two peroxyl radicals, the bisphenol **4** splits in two fragments not capable of further inhibiting the autoxidation reaction.

It is possible that the complex behavior of the investigated sulfides may be due to the instability of the quinolide peroxide formed by addition of a second peroxyl radical to the carbon linked to the sulfur substituent (**10**, Scheme 3). This adduct, characterized by the presence of two reactive moieties (-OO- and -S-) close together, might be cleaved thermally giving sulfoxides and sulfones and other products devoid of any antioxidant activity.[34]

It should be emphasized that the $n = 3$ value observed with bisphenol **7** might be consistent with the above suggestion. Actually, due to the reduced size of the methyl group in one of the *ortho* positions, attack of the second peroxyl radical to the primarily formed phenoxyl radical from **7** may occur not only at C-4 but also at C-6, thus giving the analogue of **10** as well as **11**, where sulfur and peroxide groups are isolated. In fact, **11** could be identified by ESI-MS at 456 m/z by negative ion detection mode.

The formation of sulfoxides and sulfones might arise, beside from decomposition of quinolide peroxides such as **10**,[34] also from direct reaction of peroxyl radicals with the starting sulfides, as has been reported previously by different authors.[35] Thus, competition for peroxyl radicals between the phenolic OH and the sulfur atom can give rise to stoichiometric factors shorter than expected, as, for instance, the $n = 1.7$ value found for phenol **1** and $n < 2$ observed by Ingold and co-workers[3] for sulfur analogues of vitamin E. However, this competition is not believed to be responsible for the abnormally small n coefficients of bisphenols **4**, **7**, and **9**, which are very similar despite the large difference between the k_{inh} values.

Conclusions

The kinetic and thermochemical data collected in this work demonstrate that the effect of *p*-thiyl substituents (SR) on the antioxidant properties of phenol derivatives is that of decreasing the bond dissociation enthalpy of the phenolic O−H bond and of increasing the rate constant for the reaction with peroxyl radicals. The enhanced activity as chain-breaking antioxidants of phenols *para*-substituted with a SR group is, however, substantially smaller than that of the corresponding *p*-methoxy phenols. This result, together with recent findings[36] on seleno-tocopherol indicating that the replacement of the chromanolic oxygen with selenium does not improve neither the BDE(O−H) nor the k_{inh} value with respect to α-tocopherol, suggest that the chain-breaking antioxidant efficacy of phenols *para*-substituted with XR groups decreases in the order $X = O > S > Se$. However, it should be emphasized that this holds for initiated oxidations at low temperature, whereas spontaneous oxidations proceeding more slowly or at higher temperatures might be inhibited efficiently also by sulfur- or selenium-containing phenols as a result of their ability to behave as preventive antioxidants by decomposing hydroperoxides to alcohols.

By investigating phenols **8** and **9**, we have also been able to measure the contribution of an *ortho* SR group to the antioxidant activity of phenols and to evaluate the importance of the intramolecular O−H··· SR hydrogen bonding in determining the properties of such molecules. The present data imply that the intramolecular hydrogen bond of the phenolic OH proton to the adjacent SMe group is weaker than that to an OMe group, in contrast with DFT calculations carried out on a number of *ortho*-substituted phenols.[37]

At variance with what is observed with SR groups, substitution of the *para* position with oxygenated sulfur groups does not lead to any improvement (SO_2R substituents) of the antioxidant activity of phenols or only to a very small improvement (SOR groups).

Some important points concerning the radical chemistry of sulfur-containing phenols remain to be better clarified, in particular the fate of oxidized products deriving from the reaction with peroxyl radicals. It is worth to be noted that product studies are only seldom reported in the characterization of new antioxidants, although this piece of information may be crucial for practical purposes.

Experimental Section

Matherials. Sulfide **1** was prepared by methylation 2,6-di-*tert*-butyl-4-mercaptophenol with methyl iodide.[38] The mercaptophenol was obtained by $LiAlH_4$ reduction of the corresponding *N*-thiophthalimide.[39]

Sulfide **4** was prepared reacting 2,6-di-*tert*-butylphenol with sulfur and potassium hydroxide in refluxing ethanol as previously reported.[38] Sulfoxides **2** (racemic mixture) and **5** and sulfones **3** and **6** were prepared from the corresponding sulfides by oxidation with *m*-CPBA in dichloromethane.

2,4-Di-*tert*-butyl-6-methylthiophenol (**8**) was prepared by reacting 2,4-di-*tert*-butylphenol with sulfur monochloride to obtain the isolable intermediate 2,2′-trithiobis(2,6-di-*tert*-butylphenol), which was reduced with zinc in acidic conditions to give 3,5-di-*tert*-butyl-2-hydroxybenzenethiol.[40] This compound was treated with io-

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[31] BDE and k_{inh} values have been taken from refs 13 and 18 for X = H, Me, and OMe and from ref 33 for $X = CH{=}CHC_6H_3(OMe)_2$. The equation of the regression line is $BDE = 91.34 - 2.80 \text{ Log } k_{\mathrm{inh}}$.

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domethane in 2-propanol/NaOH, and after chromatography on silica gel (petroleum ether/ethyl acetate 8/2) **8** was obtained.[41]

All other compound used in the present investigation were commercially available. Solvents of the highest purity grade were used as received. Styrene was percolated on alumina before each experiment to remove traces of inhibitor.

Kinetic Measurements. The rate constants for the reaction of the title compounds with peroxyl radicals were measured by following the autoxidation of either cumene or styrene at 30 °C using as initiator AMVN (5×10^{-3} M). The reaction was been performed in a oxygen uptake apparatus built in our laboratory and based on a differential pressure transducer. The entire apparatus was immersed in a thermostated bath that ensured a constant temperature within ±0.1 °C. In a typical experiment, an air-saturated cumene (7.1 M) or styrene (4.2 M) solution in chlorobenzene containing the antioxidant was equilibrated with the reference solution containing an excess of α-tocopherol (1×10^{-3} to 1×10^{-2} M) in the same solvent at 30 °C. After equilibration, a concentrated chlorobenzene solution of AMVN was injected in both the reference and sample flasks, and the oxygen consumption in the sample was measured, after calibration of the apparatus, from the differential pressure recorded with time between the two channels. This instrumental setting allowed us to have the N_2 production and the oxygen consumption derived from the azo-initiator decomposition already subtracted from the measured reaction rates. Induction period lengths (τ) were determined (eq 14) using an integration procedure suggested by Roginsky et al.[20]

$$\tau = \int_{\infty}^{0} \{1 - (R/R_0)^2\}\, \mathrm{d}t \qquad (14)$$

Initiation rates, R_i, were determined for each condition in preliminary experiments by the inhibitor method[18] using α-tocopherol as reference antioxidant: $R_i = 2[\alpha - \mathrm{TOH}]/\tau$. Because reaching the steady state conditions, after injecting the azo-initiator in the reaction vessel, requires some time during which the reaction is slightly slowed, the zero time of the reaction was extrapolated using the trace obtained in the absence of antioxidant.

EPR and Thermochemical Measurements. Deoxygenated benzene solutions containing the phenols (0.01−0.001 M) and di-*tert*-butyl peroxide (10% v/v) were sealed under nitrogen in a suprasil quartz EPR tube. The sample was inserted at room temperature in the 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 spectrometer equipped with a 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 ($g = 2.00258$).

When using mixtures of BHT and one of the investigated phenols, the molar ratio of the two equilibrating radicals was obtained from the EPR spectra and used to determine the equilibrium constant, K_e. Different concentration ratios of starting phenols were used in order to check if the equilibrium is reached. Spectra were recorded a few seconds after starting to irradiate in order to avoid significant consumption of the phenols during the course of the experiment.

Relative radical concentrations were determined by comparison of the digitized experimental spectra with computer simulated ones as previously described.

FT-IR Measurements. The FT-IR spectra were measured from 4000 to 600 cm^{-1} using a spectrometer having a resolution of 1.0 cm^{-1}. Tetrachloromethane solutions (0.05−0.01 M) of phenols **8** and **9** were examined in a sealed KBr cell with 0.5 mm optical path.

MS Analysis. An acetonitrile solution of sulfides **1**, **4**, **7**, **8**, and **9** (1×10^{-3} M) was stirred under air at 60 °C in the presence of AIBN (5×10^{-2} M). Aliquots of the reaction mixtures were diluted 1:10 with MeOH, cooled to 0 °C, and analyzed by mass spectrometry using electrospray ionization (ESI) by direct liquid injection at a flow rate of 10−20 μL/min. The spectrometer employed was equipped with a single quadrupole analyzer. The most appropriate instrumental settings were as follows: ESI type, positive and negative ions; desolvatation gas (N_2), 242 L/h; cone gas (skimmer), 33 L/h; desolvatation temperature, 120 °C, source block temperature, 80 °C; capillary voltage, 3.00 kV; cone voltage, 22 V; hexapole extractor, 3 V.

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Supporting Information Available: Detailed kinetic results for the determination of k_{inh} and n values. This material is available free of charge via the Internet at http://pubs.acs.org.

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