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Antioxidant Activity of *o*-Bisphenols: the Role of Intramolecular Hydrogen Bonding

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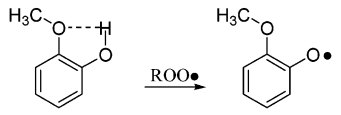
A kinetic and thermodynamic investigation on the antioxidant activity of 2,2′-methylenebis(6-*tert*-butyl-4-methylphenol) (**2**), 2,2′-ethylidenebis(4,6-di-*tert*-butylphenol) (**3**), and 4,4′-methylenebis(2,6-di-*tert*-butylphenol) (**4**) are reported. EPR studies of the equilibration between **3** or **4** and a reference phenol, and the corresponding phenoxyl radicals, allowed us to determine the O−H bond dissociation enthalpy (BDE) of the O−H bond as 81.2 and 81.1 kcal/mol in **3** and **4**, respectively. Despite this similarity, the absolute rate constants for the reaction with peroxyl radicals, determined by autoxidation studies under controlled conditions, indicate that the *o*-bisphenols **2** and **3** behave as excellent antioxidants while the *p*-bisphenol **4** is less effective by a factor of 64 and 22, respectively. FT-IR spectroscopy and product studies suggest that the very good antioxidant activity of the *o*-bisphenols largely arises from both the reduced steric crowding about the hydroxyl group and the stabilization of the aroxyl radical due to the formation of an intramolecular hydrogen bond between the residual OH and the oxygen radical center.

Introduction

Phenolic compounds such as α-tocopherol, butylated hydroxytoluene (BHT), and butylated hydroxyanisole (BHA) represent the major family of both natural and synthetic antioxidants.[1] Their activity is due to the lability of the hydrogen atom of the phenolic OH that can be easily abstracted by peroxyl radicals sustaining the autoxidative chain reaction, thus forming a relatively unreactive aryloxyl radical that wanders around until reacting with another peroxyl radical, thus interrupting a second radical chain.[2] The majority of plants also contain polyphenolic antioxidants characterized by the presence of several reactive OH groups and by complex structures that make difficult to envisage an unequivocal correlation between their antioxidant activity and the molecular structure.[3]

To make predictions on the antioxidant behavior of this kind of natural radical scavengers, knowledge is required not only of the effect of the various substituents in the aromatic ring[4] but also of the contributions due to the formation of intramolecular hydrogen bonds between nearby functional groups in both phenol and phenoxyl radical. During the past few years, the interest toward the effect of intramolecular interactions on the reactivity of phenolic function has considerably increased. Experimental studies have shown that phenolic hydrogens involved in intramolecular H-bonding are less reactive toward peroxyl radicals than free hydroxyl groups and that, in turn, their reactivity is less affected by H-bond acceptors (HBA) solvents.[5] These effects can be rationalized by considering that the H-bond stabilizes the starting phenol and that this stabilization is lost in the phenoxyl radical, so that the energy needed to abstract the hydrogen atom (i.e., the O−H BDE value) is larger than in non H-bonded phenols, as exemplified in eq 1 for 2-methoxyphenol. Moreover, the hydroxyl hydrogen is less available for giving a strong and directional H-bond with HBA solvents.



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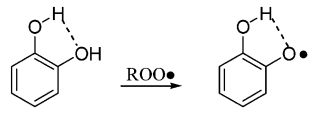

(2)

In the case of catechol derivatives, on the other hand, an intramolecular H-bond is present both in the phenol and in the phenoxyl radical (eq 2) so that the resulting

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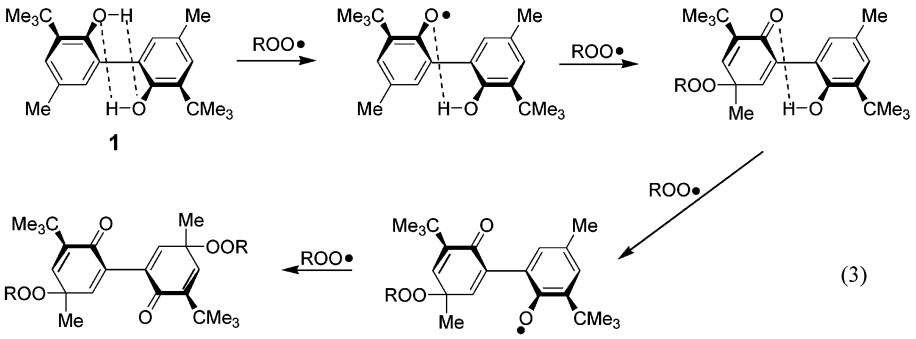
SCHEME 1

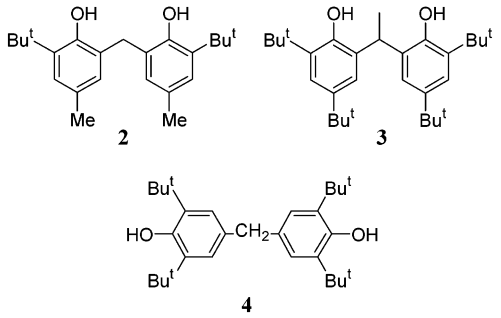


(3)

BDE value depends on their strength difference.[6] Actually, both experimental and computational evidence has been reported that the H-bond in the semiquinone radical is stronger than in the parent catechol. This lowers the BDE and increases the effect of HBA solvents on the reactivity.[6]

Only a few studies have instead been reported up to date on polyphenols whose hydroxyl groups do not belong to the same aromatic ring.[7,8] Thus, since it was of some interest to verify if cooperative effects between the various hydroxyl groups could be important also in determining the antioxidant properties of this kind of polyphenols, we have undertaken a thermodynamic and kinetic study of synthetic *o*-bisphenols, some of which are widely used as technological antioxidants. In a previous paper,[7] we examined the properties of 3,3′-di-*tert*-butyl-5,5′-dimethyl[1,1′-biphenyl]-2,2′-diol (**1**) and explained the unusually low reactivity toward peroxyl radicals of this compound as due to the formation of a twin intramolecular hydrogen bond in the starting phenol. Computations indicate that **1** adopts a *cisoid* geometry with the two aromatic rings making a dihedral angle of ca. 50° and where each of the two OH protons is hydrogen bonded to the oxygen of the other hydroxyl group. The stabilization of the bisphenol due to the twin H-bond is only partially balanced, in the corresponding phenoxyl radical, by that one due to the single hydrogen bond (Scheme 1, eq 3), so that the exothermicity of the inhibition reaction and the corresponding rate constant are lower than predictable by neglecting the effect of the intramolecular H-bonds. Experimental evidence was also obtained that the phenoxyl radical reacts with a second peroxyl radical to give a quinone adduct where the remaining OH is strongly H-bonded to the carbonylic oxygen. This intramolecular complexation, together with the unfavorable electronic effect of the cyclohexadienone substituent, renders the second phenolic OH even less reactive than the first one with the result of drastically reducing the antioxidant activity of **1** with respect to that one of related derivatives.

To better clarify the role of cooperative effects between hydroxyl groups in antioxidants containing two phenolic units, we have investigated the *o*-bisphenols **2** and **3** in which the aromatic rings are isolated by a methylene and an ethylidene bridge, respectively, and their properties have been compared with those of the *p*-bisphenol **4** and of related monophenols.



Results

Kinetic Studies. The antioxidant properties of the above derivatives were investigated by performing autoxidation experiments of an oxidizable substrate under controlled conditions at 30 °C in air-saturated solutions in the presence of small amounts of the above polyphenols or of α-tocopherol, BHT (2,6-di-*tert*-butyl-4-methylphenol), BHA (2,6-di-*tert*-butyl-4-methoxyphenol), 2,4,6-trimethylphenol (TMP) as reference chain-breaking antioxidants. The oxidation, initiated by AMVN (2,2′-azobis(2,4-dimethylvaleronitrile)), was followed by monitoring the oxygen consumption with an automatic recording gas absorption apparatus, built in our laboratory, using a commercial differential pressure transducer.[9]

Both cumene and styrene were used as oxidizable substrates since the less oxidizable cumene[10] allows an easier determination of the stoichiometric factor *n*, i.e., the number of peroxyl radicals trapped by each molecule of antioxidant,[11] while the rate constants of inhibition of the various antioxidants can be more accurately measured with styrene.[12] Almost neat cumene was used in the first series of experiments in order to increase the overall oxygen consumption and so the response of the apparatus. The induction time, was compared with that

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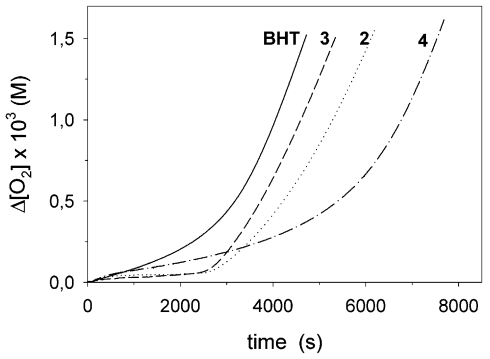

FIGURE 1. Oxygen consumption observed during the AMVN (4.93 mM) initiated autoxidation of cumene 7.1 M at 30 °C in the presence of the same amount (4.93 μM) of each antioxidant.

of BHT, each molecule of which is known to react with two peroxyl radicals.[2]

The results of these measurements, reported in Figure 1, show a strikingly different behavior between *p*- and *o*-bisphenols. Actually, the *p*-bisphenol **4** shows an induction period approximately twice as long as that of BHT, this demonstrating that **4** is capable of trapping four peroxyl radicals. Therefore, the methylene bridge completely isolates the two phenolic rings so that they behave independently one of the other.

Very different is the behavior of the other two bisphenols **2** and **3**, showing instead a first period (corresponding, more or less, to the consumption of one of the two hydroxyl groups) during which the autoxidation reaction is more strongly inhibited than by BHT or **4** and then a second period where only a weak retarding effect is observed. This means that one phenolic group is characterized by a very efficient antioxidant behavior while the second one behaves as a very poor antioxidant.

The rate constants for the reaction of the investigated bisphenols with peroxyl radicals were determined by studying the inhibited autoxidation of styrene in either chlorobenzene or *tert*-butyl alcohol at 30 °C. AMVN (4.93 mM) was used as radical initiator, and the antioxidant concentration was kept in the range from 5 to 100 μM in order to have a chain length not shorter than 10. Under these conditions, no well-defined induction period could be observed with some of the investigated compounds; thus, the values of the inhibition rate constants, k_{inh}, i.e., the rate constant for the reaction of peroxyl radicals with the antioxidant, could not be simply determined from the initial slopes of the oxygen uptake traces.[9,13] They were instead obtained with the method proposed by Darley-Usmar et al.,[14] consisting of making measurements at different antioxidant concentrations and reporting the ratio between the rates of oxygen uptake in the presence and in the absence of antioxidant $(d[O_2]/dt)_i/(d[O_2]/dt)_0$ as a function of the antioxidant concentration. Analysis of the data (see Figure 2) provides a composite rate constant k_{AH} from which k_{inh} can be calculated by using eq 4.

$$k_{AH} = \frac{k_{inh}}{(2k_t R_i)^{1/2}} \qquad (4)$$

The rate of initiation R_i was determined in separate experiments by using α-tocopherol as inhibitor under the same reaction conditions, and for the rate constant of self-termination, $2k_t$, of styrylperoxyl radicals at 30 °C, the value of 4.2×10^7 M^{-1} s^{-1} reported in the literature[11] was used.

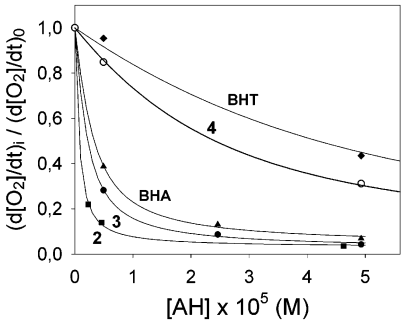

FIGURE 2. Ratio of the oxygen consumption rates measured during the autoxidation of styrene (4.3 M) initiated with AMVN (4.9 mM) at 30 °C in chlorobenzene in the presence and in the absence of a given antioxidant (AH). In the cases of **4** and **BHT**, concentrations 1×10^{-4} M of antioxidant (not shown) were also used.

TABLE 1. Inhibition Rate Constants, k_{inh}, Measured in a Chlorobenzene Solution of Styrene (4.3 M) at 30 °C and Bond Dissociation Enthalpies (BDE) of Polyphenols

antioxidant	k_{inh}[a]/M^{-1} s^{-1}	*n*	BDE/kcal mol^{-1}
2	5.0×10^5 [b]	2	
	2.0×10^3 [c]	2[d]	
3	1.7×10^5 [b]	2	81.2 ± 0.1
	1.1×10^3 [c]	2[d]	
4	7.7×10^3	4	81.1 ± 0.1
BHT	8.2×10^3	2	81.0 ± 0.1[f]
BHA	1.1×10^5 [e]		78.3 ± 0.1[f]
TMP	8.5×10^4 [e]	2	82.7 ± 0.2[f]

[a] The spread in the k_{inh} values was <±10% in all cases. [b] This rate constant and the corresponding stoichiometric factor refers to the inhibition period during which the autoxidation is strongly inhibited. [c] This rate constant refers to the second period during which the autoxidation is only slightly retarded. [d] Value assumed. [e] Taken from ref 2b. [f] Taken from ref 16.

The determined values of the inhibition rate constants, k_{inh}, of the investigated antioxidants are reported in Table 1. From these data it can be seen that the k_{inh} value for *p*-bisphenol **4** is practically identical to that of **BHT**, this being consistent with the conclusion reported above that in **4** the two antioxidant units behave independently one of the other, so that the total antioxidant effect of the bisphenol at a given concentration is equivalent to that of BHT at a concentration twice as big. The two *o*-bisphenols **2** and **3**, on the other hand, are characterized by inhibition rate constants 60 times and 20 times larger than **BHT**, respectively, during the initial part of the autoxidation, i.e., while only one of the two hydroxyl groups is consumed. The second hydroxyl group, instead, behaves as a scarcely effective inhibitor; actually, by analyzing the second part of the oxygen consumption plots (see Figure 2), the value of k_{inh} for this OH group was determined as 2.0×10^3 $M^{-1}s^{-1}$ for **2** and 1.1×10^3 $M^{-1}s^{-1}$ for **3**, respectively.[15]

The effect of a solvent acceptor of hydrogen bonds (HBA) on the antioxidant activity of these compounds

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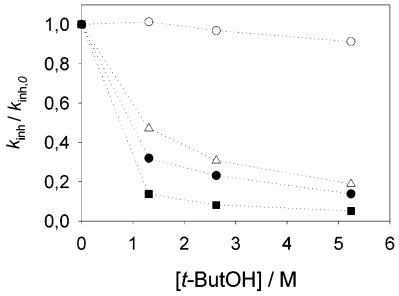

FIGURE 3. Plot of the ratio between the k_{inh} values measured at different *t*-BuOH concentrations and in the absence of *tert*-butyl alcohol: ○, BHT; △, 2,4,6-trimethylphenol (TMP); ■, **2**; ●, **3**.

was also investigated by adding to the reaction mixture variable amounts of *tert*-butyl alcohol. The observed kinetic solvent effect (KSE)[17] on the rate constant of inhibition, k_{inh}, shown in Figure 3, was negligible when using BHT as antioxidant, this being in agreement with previous results showing that solvation of the hydroxyl group of 2,6-di-*tert*-butylphenols by HBA solvents is unimportant.[18−20] The other investigated phenols and bisphenols showed instead a significant KSE that increases by increasing the *tert*-butyl alcohol concentration. It should be emphasized the fact that the kinetic solvent effect is larger for the bisphenols **2** and **3** than for 2,4,6-trimethylphenol (TMP). Actually, at the higher *tert*-butyl alcohol concentration investigated (5.24 M) the inhibition rate constant is smaller by a factor of 5.3, 7.3, and 19.6 for TMP, **3**, and **2**, respectively.

Bond Dissociation Enthalpies of the O−H Bond. The determination of the O−H bond dissociation enthalpies was done by measuring the equilibrium constant, K_e, for the hydrogen atom transfer reaction from each of the bisphenols (ArOH) and a reference phenol (Ar′OH), whose BDE value is known, to the corresponding phenoxyl radicals (eq 5) generated under continuous photolysis.[16]

$$\text{ArO-H} + \text{Ar′OH}^{\bullet} \rightleftharpoons \text{ArO}^{\bullet} + \text{Ar′OH} \qquad (5)$$

Experiments were carried out in concentrated solutions of the phenols (≥0.1 M) so that, in the calculation of K_e, the initial concentration of ArOH and Ar′OH could be used, while the relative amounts of the two radicals were determined by means of EPR spectroscopy. The BDEs for the species ArOH were obtained from eq 6 by using the known BDE (81.02 kcal/mol) of BHT used as the reference species, Ar′OH, and the experimental value of K_e, in the assumption that the entropic term can be neglected.[16]

$$\text{BDE(ArO-H)} = \text{BDE(Ar′O-H)} - RT\ln(K_e) \qquad (6)$$

While the phenoxyl radical from **2** was not persistent enough to allow us to determine the O−H bond dissociation enthalpy of the corresponding bisphenol, both **3** and **4** afforded persistent phenoxyl radicals. The EPR spectrum of **4**, centered at $g = 2.0046$, consisted of a triplet (a_H = 9.80 G) of triplets (a_H = 1.70 G) due to the methylene and meta protons, respectively. The spectrum of **3** was instead a doublet (a(1H) = 2.55 G) centered at $g = 2.0047$ showing partially resolved hyperfine structure which, by computer simulation, could be interpreted in terms of two additional doublets (a(1H) = 0.97 G and a(1H) = 0.76 G) of decets (a(9H) = 0.28 G). Since in 2,4,6-alkyl substituted phenols the sum of the two meta proton splittings is usually 3.3−3.4 G,[16] a reasonable assignment is that the larger and the smaller splittings are due to the meta protons while the 0.97 G coupling is due to the hydrogen of the ethylidene group. Such a small value implies that this hydrogen is nearly coplanar with the aromatic ring, as it should actually be expected for steric reasons. The BDE values of **3** and **4** determined with the EPR equilibration technique are reported in Table 1 together with those of the substituted phenols BHT, BHA, and TMP.

FT-IR Spectra. To investigate the solution structure of the three bisphenols **2**−**4**, their FT-IR spectra were measured from 3800 to 3200 cm^{-1} in tetrachloromethane solutions in the concentration range 0.01−0.5 M. While **4** showed in this frequency range only a single sharp line characteristic of free OH group centered at 3648 cm^{-1} similarly to BHT, both **2** and **3** showed two main absorptions, i.e., a sharp one centered at 3630 cm^{-1} and a much broader one between 3550 and 3400 cm^{-1} with maxima at 3491 and 3508 cm^{-1}, respectively. Since the IR spectra have been recorded at low concentration in order to avoid the formation of intermolecular hydrogen bonds and since the relative intensities of these absorptions are independent from the substrate concentration, it can be concluded that one of the hydroxyl groups of both **2** and **3** is free while the other one is intramolecularly hydrogen bonded. Similar conclusions have been reached by Kovac et al.,[21] who also discussed the nature of the hydrogen bonded species of **3**. In a recent DFT study on the related bis(2-hydroxyphenyl)methane, it has been similarly reported that the more stable conformation is that one where one hydroxyl proton is hydrogen bonded to the oxygen atom of the second hydroxyl group whose hydrogen is instead free.[22]

Products Studies. With the aim to better understand the origin of the large difference in the reactivity of the two hydroxyl groups of *o*-bisphenols we have also investigated by mass spectrometry the nature of the products formed from **2** during its reaction with peroxyl radicals. An ACN solution of **2** (0.03 M) containing a large excess of azo-bisisobutyronitrile (AIBN) at 50 °C was kept in an open atmosphere for ca. 30 min.[23] The crude reaction

(15) In the calculation of k_{inh}, the stoichiometric coefficient was assumed to be 2 for both the inhibited and retarded periods since the reactivity of the two hydroxyl groups is so different that they behave independently of one another.

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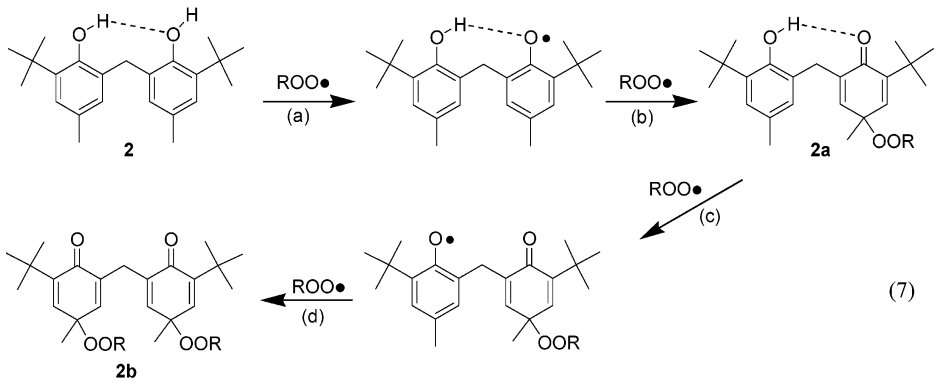
SCHEME 2



(7)

mixture was analyzed by mass spectrometry using electrospray ionization (ESI).[24]

Although the mass spectrum (see Figure 4) shows many peaks, the two larger ones are due to the addition products of peroxyl radicals ($Me_2C(CN)OO^{\bullet}$) from AIBN to the positions para to the OH groups in one (**2a**) or both (**2b**) rings. Actually, the two main signals can be seen at $m/z = 462$, attributed to the [**2a** + Na]$^+$ ion from the mono adduct, and at $m/z = 561$, attributed to the [**2b** + Na]$^+$ ion from the diadduct. Thus, the reaction mechanism exemplified in eq 7 (Scheme 2) can be reasonably postulated when peroxyl radicals are produced in the presence of the bisphenol antioxidant **2**.

Discussion

The experimental results collected in the present study indicate that the thermochemical and kinetic parameters related to antioxidant activity of the *p*-bisphenol **4** are entirely predictable on the basis of those for the parent monophenol BHT, while those for the *o*-bisphenols **2** and **3** can only be rationalized by taking into account the effects due to the formation of intramolecular hydrogen bonds both in the starting bisphenols and in the corresponding phenoxyl radicals.

Actually, in **4** both the inhibition rate constant k_{inh} and the BDE value are identical, within experimental error, to those of BHT while the stoichiometric factor n is twice as big, this suggesting that the two phenolic units behave independently one of the other, the only difference with respect to BHT being due to the different number of hydroxyl groups. On the other hand, in the *o*-bisphenols **2** and **3** the two hydroxyl groups show a very different reactivity toward peroxyl radicals, the first OH to be consumed being more reactive than the OH group of BHT by a factor of 60 and 20 and the second OH being less reactive by a factor of 4 and 7, respectively. One of the reasons why the reactivity of one OH group of **2** and **3** ($k_{inh} = 5.0 \times 10^5$ and 1.7×10^5 M^{-1} s^{-1}, respectively) is much larger than that of BHT or **4** ($k_{inh} = 8.2 \times 10^3$ and 7.7×10^3 M^{-1} s^{-1}) is that the hydroxyl groups in the former derivatives are less sterically hindered than in 2,6-di-*tert*-butyl phenols and therefore more easily accessible to the attack of peroxyl radicals. However, this cannot be the only explanation since the two *o*-bisphenols are even more reactive than 2,4,6-trimethylphenol ($k_{inh} = 8.5 \times 10^4$ M^{-1} s^{-1}) where the hydroxyl group is less hindered than in **2** and **3**. Moreover, the huge difference between the inhibition rate constants of the two phenolic units in the same bisphenol cannot be rationalized in terms of steric crowding. Thus, some other effect must be responsible for the behavior of these *o*-bisphenols. An answer to this question is suggested by vibrational spectroscopy since, as discussed above, the FT-IR spectra of **2** and **3** recorded in CCl_4 show in both cases the simultaneous presence of a free (at 3630 cm^{-1}) and a hydrogen-bonded OH group (at about 3500 cm^{-1}), this behavior being analogous to that found with catechols.[5,6] Therefore, similarly to catechols,[5c] a reaction mechanism (see eq 7, Scheme 2) can be suggested involving the initial hydrogen atom abstraction from the free OH group of the bisphenol (step a) to give a phenoxyl radical where the remaining hydroxyl group is intramolecularly hydrogen bonded to the radical oxygen. Since both theoretical and experimental evidence has been reported that an H-bond to a radical center is stronger than to a bivalent oxygen,[5,6] this reaction step should be more exothermic than predictable only on the basis of substituent effects.

To obtain a qualitative evaluation of the gain in the exothermicity of the process due to H-bond formation in the radical, the BDE values for **3** and **4** were calculated for one of the phenolic units by means of the group additivity rule[25] using the parameters for the various substituents obtained[4] by means of the same EPR technique used in the present investigation. Under the reasonable assumption that the contribution due to the substituted benzyl group *ortho* or *para* to the hydroxyl

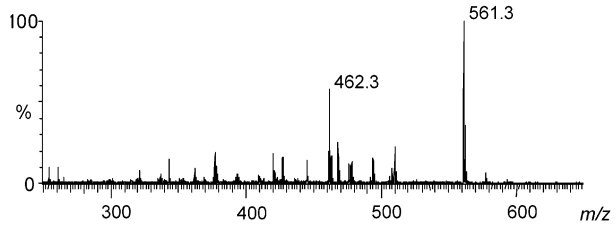


FIGURE 4. Electrospray ionization mass spectrum (ESI-MS) of the products formed by reacting the bisphenol **2** with AIBN under air at 50 °C for 1 h.

(23) Experiments were performed at high concentration of antioxidant and azoinitiator (AIBN) in the absence of any oxidizable substrate in order to simplify the MS spectra.

(24) Whitehouse, C. M.; Dreyer, R. N.; Yamashita, M.; Fenn, J. B. *Anal. Chem.* **1985**, *57*, 675.

(25) Borges dos Santos, R. M.; Martinho Simões, J. A. *J. Phys. Chem. Ref. Data* **1998**, *27*, 707−739.

group is identical to that of a methyl group[26] and by neglecting the contribution from hydrogen bonding both in the starting phenol and in the related phenoxyl radical, the BDE values of the **3** and **4** are computed as 82.2 and 81.1 kcal/mol, respectively. Being the corresponding experimental BDE values 81.2 and 81.1 kcal/mol, the lower than expected bond dissociation enthalpy measured in **3** is attributed to the different strength of the intramolecular hydrogen bonds in the bisphenol and in the corresponding phenoxyl radical, since in both species only one hydrogen bond is present. Thus, the H-bond in the radical should be 1.0 kcal/mol larger than in the parent **3**, in good agreement to what found with catechols where the energy difference of the H-bond in the semiquinone radical and in the parent diol is 0.9 kcal/mol.[5c] In **2**, where the additivity rule provides a BDE value of 82.4 kcal/mol, no comparison can be made with the unavailable experimental datum, but it seems likely that similar considerations hold. It is worth to point out that, both in biphenols and in catechols, the determined H-bond difference between the radical and the parent derivative does not not exceed ca. 1.0 kcal/mol, in contrast with DFT calculations predicting instead a difference of several kcal/mol for the H-bond in the two species. Actually, the computational estimate of the intramolecular H-bond in phenols bearing a OMe or OH substituent is about 4 kcal/mol while that one in semidione radical is ca. 7−9 kcal/mol.[5,27] It seems likely, on the basis of the present results, that these calculations overestimate the strength of the H-bond to a radical oxygen. Support to this point of view is provided by a recent spectroscopic study on the ability of of nitroxide radicals as hydrogen bond acceptors, indicating that these oxygen centered radicals give with alcohols H-bonds of strength similar to that of ethers and esters, i.e., 4.0−5.5 kcal/mol.[28]

An additional demonstration of the similarity between the *o*-bisphenols **2** and **3** and catechols is provided by the effect of a hydrogen bond acceptor solvent such as *tert*-butyl alcohol on the rate for the reaction with peroxyl radicals. Figure 3 shows that this reaction is slowed by the HBA solvent more than in the case of the sterically crowded 2,6-di-*tert*-butyl phenols but also than in the 2,4,6-trimethyl phenol (TMP), where the O−H group is less hindered than in **2** and **3**. We attribute this strong kinetic solvent effect, similar to that experienced by catechols,[5] to the fact that in *o*-bisphenols the solvent can better solvate the hydrogen atom of the free hydroxyl group that is made more acidic than in simple phenols by the complexation of its oxygen atom by the other OH group.

It can be therefore concluded that one of the OH group of the *o*-bisphenols **2** and **3** is much more reactive toward peroxyl radicals than that of BHT or those of the para-substituted bisphenol **4**, both because one of the ortho substituents is less bulky than the *tert*-butyl group, this making easier the approach of attacking radicals to the hydroxyl hydrogen atom and because the stabilization of the phenoxyl radical is larger than that one of the parent phenol due to the formation of a stronger intramolecular hydrogen bond.

The much lower reactivity of the second hydroxyl group, on the other hand, can be easily explained if referring to the reaction scheme shown in eq 7 (Scheme 2). The diamagnetic adduct **2a**, obtained by addition of a second peroxyl radical (step b) to the primarily formed phenoxyl radical (step a), contains an OH group strongly intramolecularly hydrogen bonded to the carbonyl group on the other ring. The reaction of this adduct with a third peroxyl radical (step c) implies a considerable loss of energy since the resulting oxygen centered radical does not contain any intramolecular hydrogen bond. The hydrogen atom abstraction from the second hydroxyl group, being energetically unfavorable, is thus expected to be quite slow as experimentally found.

In conclusion, in *o*-bisphenol antioxidants such as **2** and **3**, as well as in the previously reported **1**,[7] the thermochemistry and the kinetics of the reactions with peroxyl radicals are largely determined by the formation of intramolecular hydrogen bonds both in the phenols themselves and in the related aroxyl radicals. These intramolecular interactions, which can either increase (as in **2** and **3**) or decrease (as in **1**) the antioxidant activity of polyphenols should be taken into account in order to correctly predict the antioxidant behavior of the more complicated natural polyphenols.

Experimental Section

Materials. All compounds used in the present investigation, including **2**−**4** (Aldrich), were commercially available. Solvents of the highest purity grade were used as received.

Autoxidation Experiments. Autoxidation experiments were performed in a two-channel oxygen uptake apparatus, based on a Validyne DP 15 differential pressure transducer that has already been described elsewhere.[9] The entire apparatus was immersed in a thermostated bath which ensured a constant temperature within ±0.1 °C.

In a typical experiment, an air-saturated chlorobenzene solution of either styrene or cumene containing the antioxidant mixture (2.5×10^{-5}−1.5×10^{-4} M) was equilibrated with the reference solution containing an excess of α-tocopherol (1×10^{-3}−1×10^{-2} M) in the same solvent at 30 °C. After equilibration, a concentrated chlorobenzene solution of AMVN (final concentration 4.9×10^{-3} M) 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. Initiation rates, R_i, were determined for each conditions in preliminary experiments by the inhibitor method using α-tocopherol as reference antioxidant: $R_i = 2[\alpha\text{-tocopherol}]/t$.

Cumene[10] was used as oxidizable substrate since this hydrocarbon is characterized by lower rate constants with respect to styrene both of propagation, $k_p = 0.18\ M^{-1}\ s^{-1}$, and of termination of the oxidative chain, $2k_t = 1.5 \times 10^4\ M^{-1}\ s^{-1}$. Thus, the difference between the slopes of the inhibited and uninhibited traces of the oxygen consumption diagram, being more evident, allows an easier determination of the stoichiometric factor *n*, i.e., the number of peroxyl radicals trapped by each molecule of antioxidant.[11] Styrene, $k_p = 41\ M^{-1}\ s^{-1}$, $2k_t = 4.2 \times 10^7\ M^{-1}\ s^{-1}$,[12] was used instead in order to

(26) The additive contributions of the *o*-CH_2Ar and CHMeAr groups of **2** and **3** have been assumed to be similar to that of a methyl rather than of a *tert*-butyl group since the steric repulsion between CH_2Ar and CHMeAr (if properly oriented) and the OH group is comparable to that one between the OH and the methyl groups.

(27) Zhang, H. Y.; Sun, Y. M.; Wang, X. L *Chem. Eur. J.* **2003**, *9*, 502−508.

(28) Franchi, P.; Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *ChemPhysChem* **2002**, *3*, 789−793.

determine the rate constants of inhibition of the various antioxidants since, with this substrate, the oxidative chain has a significant length even during the induction period during which the autoxidation reaction is inhibited.

FT-IR Measurements. The FT-IR spectra were measured from 4000 to 3000 cm^{-1} using a Nicolet Protégé 460 spectrometer having a resolution 0.4 cm^{-1}, connected with a Claind CO_2-PUR air purifier. Tetrachloromethane solutions of the phenols **2**−**4** and BHT in the concentration range 0.01−0.05 M were examined in a sealed KBr cell with 0.5 mm optical path.

MS Analysis. A 1×10^{-3} M acetonitrile (ACN) solution of bisphenol **2** was stirred under air at 333 K for 60 min in the presence of 6.8×10^{-2} M of α,α′-azoisobutyronitrile (AIBN). Reaction time was chosen on the basis of inhibited autoxidation experiments so as to correspond approximately to the second half of the inhibited period. Aliquots of the reaction mixture were diluted 1:10 with ACN/MeOH 1:1, cooled to 20 °C, and analyzed by mass spectrometry using electrospray ionization (ESI) by direct liquid injection at flow rate of 10−20 μL/min. The instrument employed was a Micromass ZMD spectrometer equipped with a single quadrupole analyzer and a Z-spray ionspray source. The most appropriate instrumental settings were as follows: ESI type, positive 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.

Determination of the O−H BDE Values. The bond dissociation enthalpies of the O−H bond were obtained from the equilibrium constants K_e (eq 6) measured by EPR spectroscopy. These measurements were carried out by introducing in the EPR cavity degassed benzene solutions of mixtures of a phenol (ca. 0.1 M) and di-*tert*-butylperoxide and by photolyzing the solution with the unfiltered light from a high-pressure 500 W mercury lamp in order to generate a sufficiently high steady-state concentration of phenoxyl radicals. The determination of the relative radical concentrations was made either by integration of the EPR signals or by computer simulation of the spectra, as reported in previous papers.[16]

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