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JOC*Article*

Naphthalene Diols: A New Class of Antioxidants Intramolecular Hydrogen Bonding in Catechols, Naphthalene Diols, and Their Aryloxyl Radicals

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1,8-Naphthalenediol, **5**, and its 4-methoxy derivative, **6**, were found to be potent H-atom transfer (HAT) compounds on the basis of their rate constants for H-atom transfer to the 2,2-di(4-*t*-octylphenyl)-1-picrylhydrazyl radical (DOPPH$^{\bullet}$), $k_{ArOH/DOPPH^{\bullet}}$, or as antioxidants during inhibited styrene autoxidation, $k_{ArOH/ROO^{\bullet}}$, initiated with AIBN. The rate constants showed that **5** and **6** are more active HAT compounds than the *ortho*-diols, catechol, **1**, 2,3-naphthalenediol, **2**, and 3,5-di-*tert*-butylcatechol, **3**. Compound **6** has almost twice the antioxidant activity, $k_{ArOH/ROO^{\bullet}} = 6.0 \times 10^6$ M^{-1} s^{-1}, of that of the vitamin E model compound, 2,2,5,7,8-pentamethyl-6-chromanol, **4**. Calculations of the O−H bond dissociation enthalpies compared to those of phenols, (ΔBDEs), of **1**−**6** predict a HAT order of reactivity of **2** < **1** < **3** ≈ **4** < **5** < **6** in general agreement with kinetic results. Calculations on the diols show that intramolecular H-bonding stabilizes the radicals formed on H-atom transfer *more* than it does the parent diols, and this effect contributes to the increased HAT activity of **5** and **6** compared to the activities of the catechols. For example, the increased stabilization due to the intramolecular H-bond of **5** radical over **5** parent of 8.6 kcal/mol was about double that of **2** radical over **2** parent of 4.6 kcal/mol. Linear free energy plots of log $k_{ArOH/DOPPH^{\bullet}}$ and log $k_{ArOH/ROO^{\bullet}}$ versus ΔBDEs for compounds **1**−**6** along with available literature values for nonsterically hindered monophenols placed the compounds on common scales. The derived Evans−Polanyi constants from the plots for the two reactions, $\alpha_{DOPPH^{\bullet}} = 0.48 > \alpha_{ROO^{\bullet}} = 0.32$, gave the expected order, since the ROO$^{\bullet}$ reaction is more exothermic than the DOPPH$^{\bullet}$ reaction. Compound **6** is sufficiently reactive to react directly with oxygen, and it lies off the log $k_{ArOH/ROO^{\bullet}}$ versus ΔBDE plot.

Introduction

The reactions of oxygen-centered radicals, such as peroxyls R−O−O$^{\bullet}$, with biological molecules *in vivo* are implicated in various degenerative diseases,[1] such as cancer, heart disease, inflammation, and the aging process.[2] Consequently, the mechanism and activities of natural and synthetic antioxidants continue to receive a great deal of attention. α-Tocopherol, the natural phenolic antioxidant which is the main lipid-soluble chain-breaking antioxidant in human blood,[3] is commonly used as a standard for comparison with the antioxidant efficiencies of synthetic phenolic antioxidants. The antioxidant activities of phenols are best evaluated by determination of the rate constants for H-atom abstraction from the phenolic groups by peroxyl radicals.[4]

Active antioxidants of the polyalkylchromanol class (e.g., vitamin E) owe their activity to a combination of electronic, steric, and stereoelectronic effects which lower the bond dissociation enthalpy (BDE) of the O−H bond of the phenol and consequently increase the rate of its reaction with peroxyl radicals.[4] Interest in "maximizing" the antioxidant activity of phenols led to the development of a pentamethylfuran analogue of α-tocopherol which increased the stereoelectronic effect by providing better overlap of the para ether oxygen's p-orbital with the aromatic ring in the intermediate phenoxyl radical formed by reaction with peroxyls. This increased the antioxidant activity by a factor of 1.8 over those of chromanols of the α-tocopherol (vitamin E) class.[4a] Fur-

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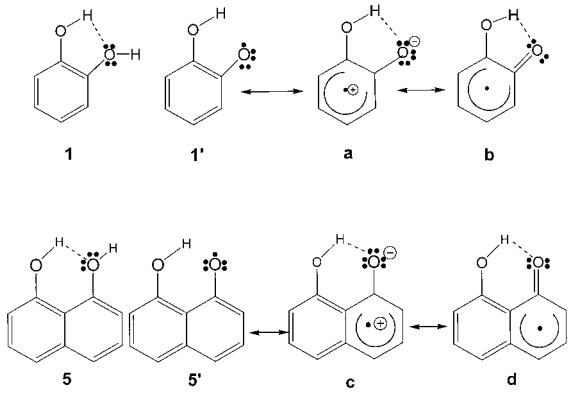
ther flattening of the furan ring did not produce any additional effect.[5] However, increased stabilization of the incipient ArO• radical by incorporating the furan ring into the α-naphthol aromatic system produced an antioxidant 10 times more active than vitamin E.[6]

The search for new structural features which increase the antioxidant activities of phenols is of significance to biomedicine because of the potential development of new protective antioxidants and to chemistry because of continuing interest in the relationship between structure and reactivity. In this connection, there is considerable evidence that intramolecular H-bonding in the catechol ring system has a pronounced effect on antioxidant activity. Earlier, we found that catechols are very active antioxidants, 3,5-di-*tert*-butylcatechol having an antioxidant activity ($k_{ArOH/ROO•}$) one-half that of α-tocopherol.[7] The key structural feature is the intramolecular hydrogen bond, since recent calculations[8] and experiments[9] have both shown that the H-bond stabilizes the *o*-semiquinone radical by about 4 kcal/mol more than it does the parent catechol. A very large class of natural compounds known as *flavonoids* contain the catechol structure, and there are several reviews emphasizing the antioxidant properties of these polyphenols.[10] Furthermore, there is theoretical[11] and experimental[12] evidence linking the antioxidant activities of flavonoids to their catechol systems. This kind of structure also occurs in catechol amines such as L-dopa and dopamine, which are reported to have both toxic and antioxidant effects,[13] in catechol steroids, for which effective antioxidant activity was found in lipoproteins,[14] and in rat liver microsomes.[15] However, both catechols and 1,4-hydroquinones have associated toxic properties in biological systems. The cytotoxicity appears to be due to two processes. Redox cycling between a semiquinone and quinone results in the formation of superoxide,[16] and quinone methides derived from 4-alkylcatechols cause damage through alkylation of cellular proteins and DNA.[17]

SCHEME 1



As part of a program to design and test new antioxidants, we considered the 1,8-naphthalenediol system to be a promising starting point for three reasons. First, the corresponding aryloxyl radical is expected to be stabilized by hydrogen bonding in a manner similar to that in the semiquinone radical from catechol, although the ring size containing the H bond differs (six-member versus five-member). Second, the naphthalene ring system is expected to provide additional stabilization of the H-bonded intermediate, and third, this system cannot form a quinone in the same way as catechols, so the toxicity shown by some quinones should be absent. The relationships between the structures are shown in Scheme 1. It is postulated that the increased stabilization of the semiquinone radical, **1′**, compared to that of the parent, **1**, is due to the increase in strength of the intramolecular H-bond induced by dipolar **a** and keto−enol **b** contributions to the radical's structure. Similar interactions are expected to be at least as strong in structures **c** and **d** from the 8-hydroxy-1-naphthyloxyl radical, **5′**, formed from parent compound **5**.

At this time, we report on the following: (a) synthesis of 4-methoxy-1,8-naphthalenediol, **6**, a new powerful hydrogen atom transfer agent (HAT); (b) the H-atom donating ability of antioxidants **5** and **6** ($k_{ArOH/DOPPH•}$) toward the 2,2-di(4-*t*-octylphenyl)-1-picrylhydrazyl (DOPPH•) radical and the antioxidant activities ($k_{ArOH/ROO•}$) of these naphthalenediols compared to catechols and typical monophenolic antioxidants; and (c) calculations of bond dissociation enthalpies (BDEs) of naphthalenediol systems, some selected catechols, and typical phenolic antioxidants.

Results

1. Syntheses. Synthetic schemes for the target molecules **5** and **6** are given in Scheme 2. The 1,8-naphthalenediol, **5**, a known compound, was readily prepared

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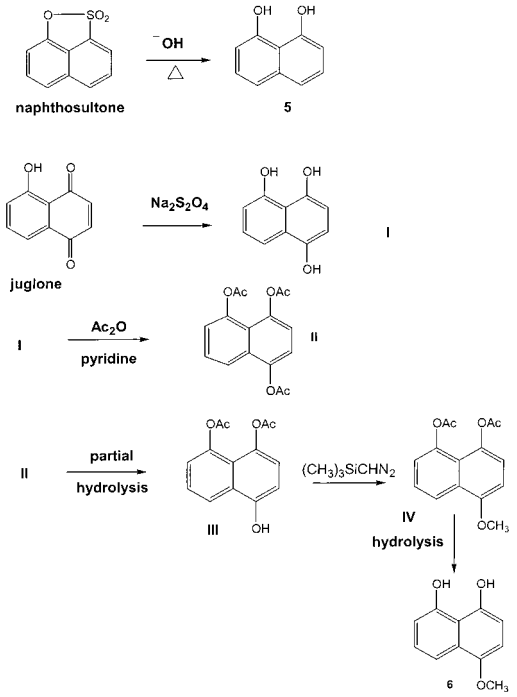
SCHEME 2



from naphthosultone, as shown. The 4-methoxy-1,8-naphthalenediol, **6**, is a new compound, and the natural product *juglone* is a convenient starting material for its synthesis. The latter was readily reduced to the triol intermediate, **I**, as shown, but because of the susceptibility of this compound to air oxidation, it was converted to its triacetate, **II**, by reaction with acetic anhydride in pyridine. The triacetate is stable in air. It was selectively deacetylated by enzymolysis at the 4-position to give **III**. The diacetate, **III**, was methylated to yield **IV** which was then hydrolyzed to produce the desired methoxy derivative, **6**.[18]

2. H-Atom Donating Properties and Antioxidant Activities. To determine the H-atom donating ability of the diols **5** and **6**, some catechols, and a typical hydroxychroman of the vitamin E class, we measured their reactivity toward the DOPPH• radical in hexane. The second-order rate constants, $k_{ArOH/DOPPH•}$, were obtained by following the decay of DOPPH• at 519 nm in the presence of excess antioxidant at various concentrations using a stopped-flow spectrophotometer at room temperature (eq 1).

$$ArO{-}H + DOPPH^{\bullet} \xrightarrow{k_{ArOH/DOPPH^{\bullet}}} ArO^{\bullet} + DOPPH{-}H \quad (1)$$

Under these pseudo-first-order conditions, eq 2 applies:

$$k^{s}_{exptl} = k_0 + k^{s}_{ArOH/DOPPH^{\bullet}}[ArOH] \quad (2)$$

Excellent correlation coefficients were obtained in all cases ($r^2 \geq 0.98$) from plots of k^{s}_{exptl} versus [ArOH] from which $k^{s}_{ArOH/DOPPH•}$ values were calculated (see Table 1). The naphthalenediols, **5** and **6**, are very active H-atom donors compared to catechols, such as **1**−**3**, and more active than the vitamin E model compound, **4**.[19] The activity of 2,3-dihydroxynaphthalene, **2**, is somewhat smaller than might have been expected, since the second aromatic ring might have been expected to lower the O−H bond dissociation enthalpy (BDE) in **2** compared to that in catechols **1** or **3**.

The antioxidant activities of the same six compounds, **1**−**6**, were determined by measuring absolute rate constants for reactions with peroxyl radicals, R−O−O•, using the inhibition of oxygen uptake (IOU) method. We used styrene, which is known to have several advantages as a substrate for quantitative studies of antioxidants,[4b] and controlled the rate of free radical initiation, R_i, using the azo initiator, azo-bis-isobutyrylnitrile (AIBN). The relevant reactions are given in eqs 3 and 4, and the expression for oxygen uptake is given by eq 5.

$$ArO{-}H + R{-}O{-}O^{\bullet} \xrightarrow{k_{ArOH/ROO^{\bullet}}} Ar{-}O^{\bullet} + R{-}O{-}OH \quad (3)$$

$$Ar{-}O^{\bullet} + R{-}O{-}O^{\bullet} \xrightarrow{fast} \text{nonradical products} \quad (4)$$

$$-d[O_2]/dt = k_p/k_{ArOH/ROO•}[\text{styrene}]R_i/n[Ar{-}OH] \quad (5)$$

The propagation rate constant, k_p, for the autoxidation of styrene is taken from the literature to be 41 $M^{-1}s^{-1}$ at 30 °C.[4b] The antioxidant activities are determined by evaluating the absolute rate constant for inhibition, $k_{ArOH/ROO•}$. This was done as usual[4b,6] by measuring oxygen consumed during the induction period. The rate constant for inhibition, $k_{ArOH/ROO•}$, was calculated using the integrated form of the equation for inhibited oxidation, eq 6, which in each case gave a linear plot of $\Delta[O_2]_t$ versus $-\ln(1 - t/\tau)$, where τ is the duration of the induction period.

$$\Delta[O_2]_t = -k_p/k_{ArOH/ROO•}[\text{styrene}]\ln(1 - t/\tau) \quad (6)$$

The number of peroxyl radicals trapped per molecule of antioxidant, the stoichiometric factor, n, was determined via eq 7, and the rate of initiation by peroxyl radicals, R_i, was calculated from the induction period obtained with pentamethylhydroxychroman, **4**, an antioxidant for

(18) The synthesis of the target molecule **6** was accomplished in the laboratory of G. Nicolosi and C. Rocco, CNR Instituto per lo Studio delle Sostanze Naturali (Italy) as follows: The naphthalene triol **I** on acetylation by treatment with acetic anhydride in pyridine yielded a triacetate derivative **II** which gave the expected ^{13}C and ^{1}H NMR spectra in $CDCl_3$ [δ 2.42 (6H, 2 × CH_3COO, positions 4 and 5); 2.49 (3H, 1 × CH_3COO, position 1); 7.14−7.33 (aromatic Hs at positions 2 and 3, a and b quartet); 7.19, 7.23, 7.85, and 7.89 (Hs at 6 and 8, split doublets); 7.54 (H at 7, triplet)]. This triacetate, which was stable in air, was selectively hydrolyzed at the 4 position by treatment in solution with a lipase enzyme at 40 °C. The resulting monophenol **III** was methylated with trimethylsilyldiazomethane to give the 4-methoxydiacetate derivative **IV** which gave the expected ^{1}H NMR spectrum [δ 4.03 (OCH_3); 2.41 and 2.42 (2 × CH_3COO)]. Further lipase-catalyzed hydrolysis of the latter yielded the required **6** in 70% overall yield from the triacetate. Compound **6** prepared in this way showed a prominent M+ peak (60%) at m/e = 190 with a base peak at 175 for loss of CH_3. ^{1}H NMR spectrum in deuterated acetone (TMS): δ 3.90 (3H, OCH_3); five distinct multiplets between 6.68 and 7.66 (each corresponding to one H, aromatic hydrogens); 9.69 and 10.06 (hydroxyl hydrogens). ^{13}C spectrum: 55.23 (OCH_3 removed on DEPT spectrum); 10 resolved peaks for aromatic carbons. DEPT spectra: CH groups at 104.7, 107.6, 109.8, 113.3, 126.4; quaternary carbons at 115.4, 128.4, 147.2, 148.9, and 154.4 δ.

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TABLE 1. Hydrogen Atom Donating Abilities, $k_{ArOH/DOPPH^{\bullet}}$, and Antioxidant Activities, $k_{ArOH/ROO^{\bullet}}$, of Naphthalene Diols, Catechols, and a Vitamin E Model Compound

compound	$k_{ArOH/DOPPH^{\bullet}}$ [a] ($\times 10^{-3}$ M^{-1} s^{-1})	$k_{ArOH/ROO^{\bullet}}$ [b] ($\times 10^{-6}$ M^{-1} s^{-1})	n[c]
catechol, **1**	1.8	0.55	2.3
2,3-naphthalenediol, **2**	1.3	0.02−0.04[d]	2.4
3,5-di-*tert*-butylcatechol, **3**	21	1.5	2.3
2,2,5,7,8-pentamethyl-6-hydroxychroman, **4**	7.4	3.3	(2.0)
1,8-naphthalenediol, **5**	310	4.3	1.5
4-methoxy-1,8-naphthalenediol, **6**	2000	6.0	1.1

[a] H-atom donating ability to the DOPPH$^{\bullet}$ radical in hexane at 25 °C under argon. [b] Antioxidant activities determined by the inhibited oxygen uptake method during oxidation of styrene at 30 °C, initiated by AIBN. Values for **1** and **3** are taken from ref 7. [c] Stoichiometric factors for the ArOH/ROOC reaction relative to a value of 2.0 for **4**. For compound **2**, n was determined in cumene relative to a value of 2.0 for 2,6-di-*tert*-butyl-4-methoxyphenol. [d] The $k_{ArOH/ROO^{\bullet}}$ value was estimated from the initial rate of oxygen uptake.[24]

which the stoichiometric factor, n, is known to be approximately 2.[4b]

$$R_i = n[\mathrm{Ar{-}OH}]/\tau \qquad (7)$$

The n factors for the compounds studied were determined from the induction periods measured under the same conditions as had been used for the measurement of R_i.

The antioxidant activities, $k_{ArOH/ROO^{\bullet}}$, of the naphthalenediols **5** and **6** and the other antioxidants studied in this work are given in Table 1. The value for the α-tocopherol model, **4**, is in agreement with the literature value (3.8×10^6 M^{-1} s^{-1}).[4b] The $k_{ArOH/ROO^{\bullet}}$ values for the naphthalenediols **5** and **6** show that they both are VERY active peroxyl radical traps, more active than either of the catechols and more active than the vitamin E model, **4**. The increased activity of **6** over that of the parent diol, **5**, can be attributed to the electron-supplying 4-methoxy group which is expected to weaken the phenolic O−H BDE and hence accelerate the reaction with peroxyl radicals. Unfortunately, **6** reacts directly with dioxygen, its solutions turning dark green on standing in air, yielding at least four products (TLC analysis). This "wasting" reaction with oxygen and possibly chain transfer reactions[6] are undoubtedly responsible for the unusually low stoichiometric factor found for **6** (viz. $n = 1.1$). The 2,3-naphthalenediol, **2**, is a surprisingly poor trap for peroxyl radicals and behaves only as a "retarder" under these conditions. As explained earlier,[20,21] the behavior of a retarder is quite different from that of an efficient radical trapping antioxidant. Retarders react relatively slowly with peroxyl radicals, only slightly reduce the rate of oxygen uptake, and do not give well-defined induction periods. This was the case with **2** in styrene. The stoichiometric factor for **2** had therefore to be measured in cumene which has a k_p of only 0.18 M^{-1} s^{-1} (ref 22) at 30 °C. In this substrate, even very poor peroxyl radical trapping antioxidants give well-defined induction periods.[23] The stoichiometric factor determined in this way for **2** was 2.4 (relative to 2.0 for 2,6-di-*tert*-butyl-4-methoxyphenol).[23] There was insufficient oxygen uptake in cumene to use the IOU method for determination of $k_{ArOH/ROO^{\bullet}}$ for **2**. The $k_{ArOH/ROO^{\bullet}}$ in styrene was estimated from the reduced oxygen uptake.[24]

3. Calculations. (a) Theoretical Methods. The Gaussian 98 program[25] was used for calculations of the bond dissociation enthalpies (BDEs) using the Medium Level Model 2 (MLM2).[26] In the MLM2 method, the electronic energy of the H-atom was set to its exact value, −0.500 00 hartree (1 hartree = 627.51 kcal mol^{-1}). The geometry was optimized for the parent and radical using B3LYP/6-31G(d). Applying the temperature correction of $^5/_2RT$, the enthalpy of the H-atom at 298 K is −0.497 64 hartree. Frequencies for ArOH and ArO$^{\bullet}$ were determined by the same method using B3LYP/6-31G(d), and zero-point energy and enthalpy corrections were scaled by the factor 0.9806. At the potential minimum, the single-point energy was determined using (RO)B3LYP/6-311+G(2d,-2p), where RO means restricted open-shell. The complete method for ArOH and ArO$^{\bullet}$ can be represented as (RO)B3LYP/6-311+G(2d,2p)//B3LYP/6-31G(d)/B3LYP/6-31G(d). In the cases of PMHC (compound **4**) and of compounds **7** and **8**, the locally dense basis set (LDBS) approach[8,27,28] was used to obtain the single-point energies of the parent and radical because of the large size of these species. The LDBS approach may be represented as (RO)B3LYP/LDBS//B3LYP/6-31G(d)/B3LYP/6-31G(d). This has been shown to give results which are of comparable accuracy to the balanced basis set approach, with agreement to within ±1 kcal/mol. For example, the BDE of phenol has been calculated to be 87.5 kcal/mol with both the balanced basis set and LDBS methods.

(b) Results. Calculated O−H bond dissociation enthalpies (BDEs) for O−H bonds are listed in Table 2. For

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(27) DiLabio, G. A.; Pratt, D. A.; Wright, J. S. *Chem. Phys. Lett.* **1998**, *297*, 181−186.
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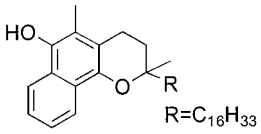
TABLE 2. Calculated Bond Dissociation Enthalpies of O−H Bonds and Hydrogen Bond Enthalpies of Phenols 1−8 in kcal/mol

compound[a]	−ΔBDE[b]	parent H-bond	radical H-bond
1	10.0	3.8	9.1
2	9.2	3.6	8.2
3	12.6	*c*	*c*
4	12.6		
5	15.7	6.2	14.8
6	20.1	6.6	15.2
7	15.8		
8	16.8		

[a] Compounds **7** and **8** were described previously.[6]



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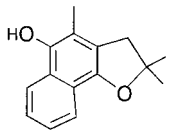

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[b] Differences in bond dissociation enthalpies: BDE(ArOH) − BDE(PhOH), where BDE(PhOH) = 87.5 kcal/mol. For compounds with two different "active sites" for hydrogen atom transfer (e.g. non H-bonded and intramolecularly H-bonded O−H), **3** and **6**, the value is for the nonbonded O−H. [c] See text.

the diols with their intramolecular hydrogen bonds, BDE values are are given for the "free", nonbonded hydroxyl group. Since the intramolecular hydrogen bonds in both the parent molecule and its radical play an important role in the behavior of these compounds, hydrogen bond strengths in both the parents and their radicals were calculated for catechol, **1**, 2,3-naphthalenediol, **2**, and the naphthalenediols **5** and **6**. For these calculations, the hydrogen bond strength is defined as the enthalpy difference for an OH group coplanar with the aromatic ring pointing away and toward the hydrogen bond accepting group. This calculation was not performed on **3** because the "away" conformer would point toward an adjacent *tert*-butyl group, and our method of calculation is known to overestimate the steric strain in such molecules.[8a] For compound **6,** the conformation with the hydroxyl group at the 1-position as the H-bond acceptor is the more stable by 0.4 kcal/mol. The results are summarized in Table 2. Optimized structures of the parent compounds **1**−**8** and the corresponding radicals are given as Supporting Information.

Discussion

It is of interest to compare the kinetic data for H-atom donating abilities and antioxidant activities of compounds **1**−**6** with the theoretical calculations of BDEs which are expected to predict the order of "activity". If one assumes that the relative $k_{ArOH/DOPPH^{\bullet}}$ and the relative $k_{ArOH/ROO^{\bullet}}$ are determined primarily by the O−H BDE, then the following order of reactivity, from the least active to most active, would be predicted: **2** < **1** < **3** ≈ **4** < **5** < **6**. Experimentally, $k_{ArOH/DOPPH^{\bullet}}$ gives **2** < **1** < **4** < **3** < **5** < **6** and $k_{ArOH/ROO^{\bullet}}$ gives **2** < **1** < **3** < **4** < **5** < **6**, in general agreement with the calculated O−H BDEs. This agreement supports a hydrogen atom transfer (HAT) mechanism as the rate-determining step for both reactions.

As already pointed out, intramolecular hydrogen bonding is important in determining the O−H BDEs of these diols and, therefore, their antioxidant activities. The intramolecular H-bonds in the naphthalenediols are stronger than those in the catechols for two reasons. First, our calculations indicate that the length of the hydrogen bond is shorter in the naphthalenediols, viz. 1.79 Å in **5** and 2.12 Å in **1**. Second, the O−H−O angle is more nearly linear in the naphthalenediols, viz. 143° in **5** and 115° in **1**. Thus, the greater HAT activities of the naphthalenediols **5** and **6** relative to the activities of **1** and **2** can be attributed, at least in part, to the greater intramolecular H-bond-induced stabilization of radicals **5′** and **6′**, relative to their parent molecules **5** and **6** (viz., for **5′**/**5**, 14.8 kcal/mol − 6.2 kcal/mol = 8.6 kcal/mol and, for **6′**/**6**, 15.2 kcal/mol − 6.6 kcal/mol = 8.6 kcal/mol) compared with the **1′**/**1** couple (9.1 kcal/mol − 3.8 kcal/mol = 5.3 kcal/mol) and the **2′**/**2** couple (8.2 kcal/mol − 3.6 kcal/mol = 4.6 kcal/mol).

The data from our Tables 1 and 2 and related literature data for a wide range of nonhindered monophenolic antioxidants[8,29−31] are summarized in the form of Evans−Polanyi[32] plots of −ΔBDE versus log $k_{ArOH/DOPPH^{\bullet}}$ (in hexane at 25 °C) and log $k_{ArOH/ROO^{\bullet}}$ (in styrene at 30 °C) (see Figure 1). According to Evans and Polanyi, for a series of similar reactions, such as $Y^{\bullet}$ + H−OAr, the activation enthalpy, E_a, will be proportional to the enthalpy of reaction, ΔH_{react}. That is, for the same radical $Y^{\bullet}$,

$$\Delta E_a = \alpha\Delta\Delta H_{react} = \alpha\Delta BDE,\ 0 < \alpha < 1 \qquad (8)$$

where ΔBDE = BDE(ArO−H) − BDE(PhO−H) and BDE(PhO−H) was calculated to be 87.5 kcal/mol. For the same $Y^{\bullet}$, the Arrhenius pre-exponential factors will be similar or even idential[33] and therefore eq 8 can be written as the following:

$$k_{ArOH}/k_{PhOH} = \exp(-\alpha\Delta BDE/RT) \qquad (9a)$$

$$\text{or } \log k_{ArOH} = \log k_{PhOH} - \alpha\Delta BDE/2.303RT \qquad (9b)$$

The value α depends on the thermochemistry of the overall H-atom transfer reactions.[34] That is, α will be small (even zero) for highly exothermic reactions and will

(29) Table S1 of ΔBDEs and rate constants for reactions of phenols with $DPPH^{\bullet}$, DOPPH, and $ROO^{\bullet}$ used in Figure 1 is available as Supporting Information.

(30) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 1744−1751.

(31) Snelgrove, D. W.; Lusztyk, J.; Banks, J. T.; Mulder, P.; Ingold, K. U. *J. Am. Chem. Soc.* **2001**, *123*, 469−477.

(32) Evans, M. G.; Polanyi, M. *Trans. Faraday Soc.* **1938**, *34*, 11−29.

(33) Foti, M.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 9440−9447.

(34) For a series of substituted phenols in a nonalkane solvent, the overall thermochemistry will, of course, contain a contribution from intermolecular hydrogen bonding. This contribution will not be a constant along the series but will be larger for phenols with electron-withdrawing (EW) substituents than for phenols with electron-donating (ED) substituents. Since EW substituents reduce and ED substituents enhance the H-atom donating abilities of phenols, an Evans−Polanyi plot for any specific reaction in a hydrogen bond accepting (HBA) solvent will have a larger slope, i.e, a larger α value, than that for the same reaction in an alkane or other non-HBA solvent. This effect will not be large for the present reactions, but it does mean that the α value for the $ArOH/ROO^{\bullet}$ reaction in styrene (a weak HBA) will be slightly enhanced over the value which would have been in a non-HBA solvent.

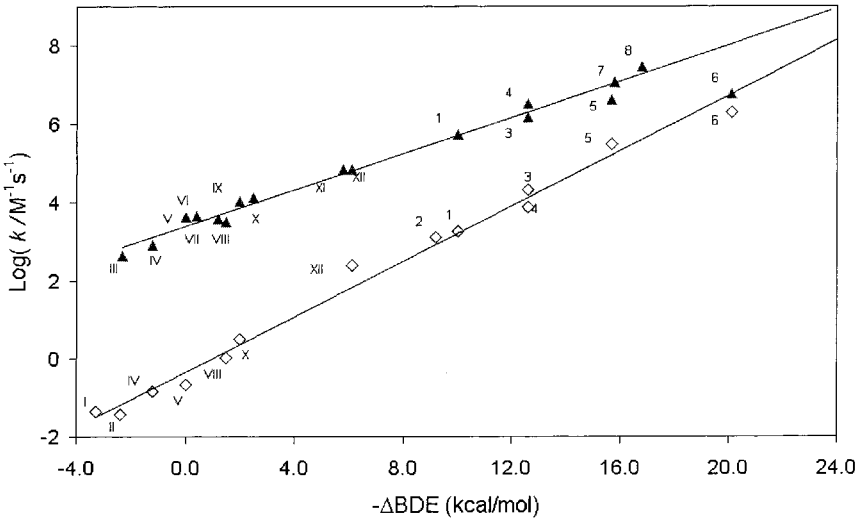

FIGURE 1. Linear free energy plots of H-atom transfer rate constants versus calculated bond dissociation energies compared to those of phenol (−ΔBDEs). Plots of log $k_{ArOH/DOPPHC}$ (◇) and log $k_{ArOH/ROOC}$ (▲) versus calculated −ΔBDEs, reference PhOH = 87.5 kcal/mol, for compounds **1**−**6** and literature data log $k_{ArOH/DPPHC}$ values for **I** = 4-CF_3−C_6H_4OH, **II** = 3,5-Cl_2−C_6H_3OH, **III** = 4-CN−C_6H_4OH, **IV** = 3-Cl−C_6H_4OH, **V** = C_6H_5OH (set = 0), **VI** = 3-Me−C_6H_4OH, **VII** = 3-MeO−C_6H_4OH, **VIII** = 4-Cl−C_6H_4OH, **IX** = 4-Me−C_6H_4OH, **X** = 4-*t*-pentyl−C_6H_4OH, **XI** = 4-OH−C_6H_4OH, **XII** = 4-MeO−C_6H_4OH, **7** = 2,5-dimethyl-2-phytyl-6-hydroxy-7,8-benzochroman, and **8** = 2,2,4-trimethyl-5-hydroxynaphtho[1,2-*b*]-2,3-dihydrofuran. Calculations for **I**, **III**−**IX**, **XI**, and **XII** are from ref 8a and were performed using the LLM method, which may be denoted as (RO)B3LYP/6-311+G(2d,2p)//AM1/AM1. For compound **II**, the BDE was estimated using the activity scheme from ref 8a. For compound **X**, the calculated BDE of 4-*tert*-butylphenol from ref 8a was used. The ArOH/DPPH• rate constants for **I**−**XII** are from ref 31. The ArOH/ROO• rate constants for **I**−**XII** are from ref 30 but have been multiplied by the correction factor 2.24, as in: Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6472−6477. The value for **XI** was divided by 2 for statistical reasons. To convert rate constants from 65to 30 °C, an average E_a of 2.5 kcal/mol was used as an approximation. The ArOH/ROO• rates for **1** and **3** are from ref 7, and those for **7** and **8** are from ref 6.

increase up to a limit (presumably) of 1.0 for highly endothermic reactions. Since the N−H bond energy in DPPH−H is ∼79.6[35] kcal/mol and the O−H BDE in ROO−H is ∼88 kcal/mol, $\alpha_{DPPH•}$ is expected to be larger than $\alpha_{ROO•}$. The plots can be described by the following:

$$\log k_{ArOH/DOPPH•} = -0.33 + 0.35(-\Delta BDE),$$
$$r^2 = 0.99; \text{ yielding } \alpha_{DOPPH•} = 0.48 \quad (10)$$

$$\text{and } \log k_{ArOH/ROOC} = 3.39 + 0.23(-\Delta BDE),$$
$$r^2 = 0.98; \text{ yielding } \alpha_{ROO•} = 0.32 \quad (11)$$

As expected, $\alpha_{DOPPH•} > \alpha_{ROO•}$.

The only serious outlier in Figure 1 is the point for the reaction of ROO• radicals with compound **6** which falls well below the best line through all of the ROO•/ArOH data. Since the point for the DOPPH• + **6** reaction also falls below the best line through the DOPPH•/ArOH data, it seems probable that ΔBDE for **6** has been overestimated,[36] perhaps by as much as 2 kcal/mol; that is, the O−H BDE should probably be ∼69 kcal/mol rather than the calculated 67 kcal/mol. While such a 2 kcal/mol "adjustment" to the ΔBDE would put the DOPPH•/**6** point on the DOPPH•/ArOH line, the ROO•/**6** point would still fall below the ROO•/ArOH line. We suggest that this lower than expected reactivity of **6** toward ROO• radicals and lower stoichiometric factor (i.e. $n = 1.1$) are likely a consequence of the "wastage" of **6** in its observed direct reaction with oxygen.

In any case, our search for new antioxidants based on the 1,8-naphthalenediol system which would be more active than α-tocopherol and **4** has been successful with the parent diol, **5**. Although compound **6** with its methoxy substituent is a very active HAT agent, this compound's sensitivity to oxygen results in a lower than "expected" antioxidant efficiency. Substituents that are less electron rich than methoxy may provide derivatives of these diols which are not sensitive to direct reaction with oxygen. Such derivatives may prove to be efficient antioxidants in natural biological media where lower oxygen partial pressures prevail.[37,38]

Experimental Section

Materials and General Methods. All solvents used were of highest purity, dried over molecular sieves, and distilled just before use. The chemicals, 1,8-naphthosultone, 5-hydroxy-1,4-naphthoquinone (juglone), 2,2,5,7,8-pentamethyl-6-chromanol (PMHC, **4**), 2,3-naphthalenediol (**2**), catechol (**1**), 3,5-di-*tert*-butylcatechol (**3**), styrene, and cumene were purchased from a commercial supplier. The 2,2-di(4-*t*-octylphenyl)-1-picrylhydrazyl radical (DOPPH•) was obtained from Northern Sources, Inc.

Syntheses of Compounds 5 and 6. Compound **5** was synthesized by a modification of the literature procedure.[39] For

(35) Mahoney, L. R.; Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95,* 8610−8614.

(36) It has been observed before that calculated O−H BDEs in very electron rich phenols are smaller than actual values (Pratt, D. A.; DiLabio, G. A.; Brigati, G.; Pedulli, G. F.; Valgimigli, L. *J. Am. Chem. Soc.* **2001**, *123*, 4625−4626) but in other electron rich phenols there was agreement between calculated and measured values (de Heer, M. I.; Korth, H.-G.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 6969−6975).

(37) Burton, G. W.; Ingold, K. U. *Science* **1984**, *224*, 569−573.

(38) Barclay, L. R. C.; Vinqvist, M. R. *Free Radical Biol. Med.* **2000**, *28*, 1079−1090.

convenience and safety, the reaction was carried out in a deep (12 cm × 4 cm) stainless steel cylinder surrounded by an electrically heated jacket and fitted with a thermocouple for temperature control. A mechanically stirred mixture of potassium hydroxide (15 g) and sodium hydroxide (15 g) was melted at 300 °C in an argon atmosphere. The naphthosultone, 5 g, was added in small portions, and the resulting dark liquid was stirred for about 30 min. This product was then poured onto aluminum foil and allowed to solidify. The solid was ground into small pieces and then stirred with 200 mL of hydrochloric acid/water (1:2 v/v). The organic material was extracted with ethyl acetate (3 times, 100 mL). This solution was dried over anhydrous magnesium sulfate, and the solvent was removed on a rotatory evaporator to leave a dark liquid. Purification was effected in two stages. The crude material was dissolved in the minimum volume of hexane and chromatographed on silica gel. A dark brown band remained on the column while the product eluted with hexane/ethyl acetate (9:1 v/v). Distillation of the solvent left a pale yellow crystalline product. Recrystallization of this from hexane containing a small portion of ethanol yielded white needles (40% yield): mp 143−144°, lit.[38] mp 139−140°. The ^{1}H and ^{13}C NMR spectra were consistent with the literature.[38] The mass spectrum gave a parent mass *m/e* 160 which was the base peak.

The reduction of juglone was readily carried out in either ethyl acetate or ether by rapidly stirring a solution of it with an aqueous solution of sodium hydrosulfite under argon, and the triol 1,4,8-naphthalenetriol was isolated as described previously.[40] Compound **6** was synthesized from the triol in another laboratory.[18] Details will be reported separately.

Kinetic Methods. (a) Reactions of Phenols with DOPPH•. The stopped-flow experiments were carried out using DOPPH• on a spectrometer with a xenon 150 W arc light source. In a typical procedure, a solution of DOPPH• (~5 × 10^{-5} M) in hexane was mixed 1:1 with hexane solutions of the antioxidants of varying concentrations. For the more soluble compounds, the concentration range was 7×10^{-4} to 6×10^{-3} M, and for less soluble compounds (e.g., **5**), it was 1×10^{-4} to 9×10^{-4} M. The separate solutions were deoxygenated by bubbling with argon before each experiment. Decay of the DOPPH absorption at 519 nm was monitored over time to obtain k_{exptl} results, and from the linear plots of k_{exptl} versus concentrations, the second-order rate constants were calculated.

(b) Autoxidation/Inhibition Procedures. Autoxidations were carried out at 30 °C under 760 Torr oxygen in a dual channel oxygen uptake apparatus equipped with a sensitive pressure transducer, as described previously.[6,41] The styrene used was separated from a commercial inhibitor by rapid bulb-to-bulb distillation on the vacuum line and passed through a short column of alumina just before use. As emphasized earlier,[6] it is necessary to ensure that there is an appreciable kinetic chain length during the inhibition periods.

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Supporting Information Available: A table, S1, of ΔBDEs and rate constants of phenols with DPPH•, DOPPH•, and ROO• used in Figure 1 and Cartesian coordinates for structures of compounds **1**−**8** and their radicals optimized with B3LYP/6-31G(d). This material is available free of charge via the Internet at http://pubs.acs.org.

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(39) Poirier, M.; Simard, M.; Wuest, J. D. *Organometallics* **1996**, *15*, 1296−1300.

(40) Malesani, G.; Ferlin, M. G. *J. Heterocycl. Chem.* **1987**, *24*, 513−517.

(41) Wayner, D. D. M.; Burton, G. W. *Handbook of Free Radicals and Antioxidants in Biomedicine;* CRC Press: Boca Raton, FL, 1989; Vol III, pp 223−232.