Chain-Breaking Phenolic Antioxidants: Steric and Electronic Effects in Polyalkylchromanols, Tocopherol Analogs, Hydroquinones, and Superior Antioxidants of the Polyalkylbenzochromanol and Naphthofuran Class

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Antioxidant activities of four classes of phenols were measured by the inhibition of thermally initiated autoxidation of styrene at 30 °C. Class I, 6-hydroxypolyalkylchromans (model compounds) showed the same inhibition rate constants (k_{inh}) as their α-tocopherol analogs, in the range 1.5×10^6 M^{-1} s^{-1} to 3.8×10^6 M^{-1} s^{-1} for two methyl or ethyl groups *ortho* to the phenolic hydroxyl group. Bulky *ortho* groups *reduce* the k_{inh}, two isopropyl groups by 3-fold and 5-isopropyl-6-*tert*-butyl by 5-fold, compared to that of α-tocopherol, due to steric hindrance to the approach of peroxyl radicals. Class II, the α-naphthol derivatives, 6-hydroxy-2,5-dimethyl-2-phytyl-7,8-benzochroman (**9a**) and the corresponding chromene (**9b**), exhibit higher k_{inh} values, 4 times that of α-tocopherol. A new synthetic antioxidant, 2,3-dihydro-5-hydroxy-2,2,4-trimethylnaphtho[1,2-*b*]furan, exhibits $k_{inh} = 2.87 \times 10^7$ M^{-1} s^{-1}, 10 times that of α-tocopherol or any model compound, and is the most active phenolic antioxidant known. Class III, hydroquinones including 2,3,6-trimethylhydroquinone and the α-, β-, and γ-tocopherylhydroquinones, are 2 to 4 times less active as antioxidants than α-tocopherol, and class IV, the ubiquinones, are 8–10 times less active than α-tocopherol. The stoichiometric factors, *n*, for peroxyl radical trapping are 1.5–2.0 for phenols of classes I and II, 1.0–1.9 for ubiquinones but less than 0.5 for hydroquinones of class III due to "wasting" oxidation reactions of the latter. Antioxidant activities in solution are interpreted in terms of steric hindrance, retarding hydrogen transfer to peroxyl radicals, and electronic effects which increase k_{inh} by stabilization of the ArO· radicals. Results in styrene solution are in contrast with other data in aqueous lipid membranes where H-bonding by water on the antioxidants is a significant effect on k_{inh}.

Introduction

The activity and mechanism of action of free radical chain-breaking antioxidants, inhibitors of peroxyl radical attack on biological systems, continue to attract widespread interest as indicated in reviews.[1] Phenolic antioxidants have received particular attention since the discovery that α-tocopherol (vitamin E) is the major lipid-soluble chain-breaking antioxidant in human blood.[2] The high activities of α-tocopherol-type antioxidants have been interpreted by Ingold and co-workers in terms of steric and stereoelectronic effects stabilizing the aryloxyl radical formed in a rate-controlling inhibition reaction in which the phenol traps chain-propagating peroxyl radicals. Stabilization of the aryloxyl radical (ArO·) by optimum overlap between a 2p lone electron pair on a para ether oxygen and the aromatic π system is especially significant.[3a] This effect appears to have reached its limit with the five-membered ring in 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran where the nearly flat five-membered ring provides better overlap of the ether oxygen p orbital with the aromatic system thereby increasing the $k_{inhibitor}$ (k_{inh}) by 1.8 times that of α-tocopherol in homogeneous solution.[3a] Further flattening of the five-membered ring by incorporating a spirocyclopropyl moiety in place of geminal dimethyl does not increase the antioxidant activity.[3b] Replacement of the oxygen in the chroman ring by sulfur also did not increase the antioxidant activity; 1-thio-α-tocopherol and other related 6-hydroxythiochromans were less reactive toward peroxyl radicals than the 6-hydroxychromans.[3c]

We have undertaken an investigation of the steric and electronic effects controlling the antioxidant activities of sterically hindered phenols with the objective of designing compounds with antioxidant activities superior to those known. In this study we report on the role of steric hindrance by the determination of antioxidant activities and stoichiometric factors of the hydroxychromans having alkyl groups of varying size (methyl, ethyl, isopropyl, *tert*-butyl) *ortho* to the phenolic hydroxyl and a comparable study is made on compounds with the phytyl side chain of the vitamin E class. The investigation of electronic effects is extended to the determination of the effect of a second fused aromatic ring which would be expected to further delocalize the unpaired electron in the aryloxyl radical (ArO·) and raise the antioxidant activity. Known quantitative kinetic methods of autoxidation[1d,3a] are used to determine the hydrogen atom donating ability of phenolic antioxidants.

Four classes of compounds (I–IV) were studied, as shown in the general structures **1–12**: **1–8**, the 6-hydroxypolyalkylchromans ($R_1 = CH_3$) (referred to as model com-

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(1) For reviews see (a) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* (1986), *19*, 194–201. (b) Niki, E. *Chem. Phys. Lipids* 1987, *44*, 227–253. (c) Krinsky, N. I. *Ann. N.Y. Acad. Sci.* 1988, *551*, 17–33. (d) Barclay, L. R. C. *Can. J. Chem.* 1993, *71*, 1–16.

(2) Burton, G. W.; Joyce, A.; Ingold, K. U. *Arch. Biochem. Biophys.* 1982, *221*, 281–290.

(3) (a) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* 1985, *107*, 7053–7065. (b) Gilbert, J. C.; Pinto, M. *J. Org. Chem.* 1992, *57*, 5271–5276. (c) Zahalka, H. A.; Robillard, B.; Hughes, L.; Lusztyk, J.; Burton, G. W.; Janzen, E. G.; Kotake, Y.; Ingold, K. U. *J. Org. Chem.* 1988, *53*, 3739–3745.

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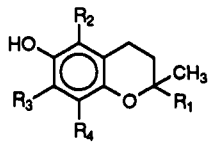
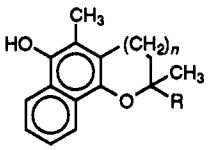
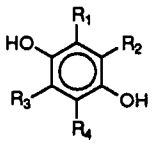
pounds) and the structurally related α-tocopherol analogs (R_1 = $C_{16}H_{33}$, phytyl); **9**, some α-naphthol derivatives, including 6-hydroxy-2,5-dimethyl-2-phytyl-7,8-benzochroman (**9a**), the corresponding chromene derivative **9b** and the related 2,3-dihydro-5-hydroxy-2,2,4-trimethylnaphtho[1,2-*b*]furan (**9c**), and some selected hydroquinone derivatives including those related to the tocopherols (**11a–c**) and the ubiquinols (**12a,b**). The latter compounds have



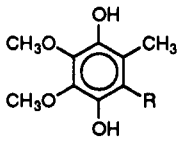
class I
(compounds 1–8)



class II
(compounds 9a–c)



class III
(compounds 10a,b,11a–c)



class IV
(compounds 12a,b)

received intense recent interest because of their activity in biological systems;[4] however, the absolute rate constants of inhibition (k_{inh}) afforded by such compounds have never been determined.

The relative hydrogen donor activities in ethanol of some compounds of class I toward a stable phenoxyl radical have been reported.[5] The present work is the first report of their antioxidant activities in a peroxyl radical chain reaction, which is more relevant to the situation of peroxidation of biological molecules.

Results

Antioxidant Activities and Stoichiometric Factors. Efficient phenolic antioxidants are well known to terminate free radical chain peroxidations by trapping two peroxyl radicals according to eqs 1 and 2, so that the so-called stoichiometric factor, n, is 2.[3a]

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

$$ROO^{\bullet} + ArO^{\bullet} \xrightarrow{fast} \text{nonradical combination products} \quad (2)$$

The expression for suppressed oxygen uptake during the inhibition period is given by eq 3.[1d,3a]

$$-\frac{d_{O_2}}{dt} = \frac{k_p}{k_{inh}} \frac{[RH]R_i}{n[ArOH]} \quad (3)$$

where k_p is the propagation rate constant of the chain reaction, k_{inh} is the rate constant of inhibition, R_i is the rate of chain initiation, and n is the stoichiometric factor.

For quantitative kinetic studies required in this investigation, a substrate with known k_p at 30 °C is selected; e.g. styrene, k_p = 41 M^{-1} s^{-1}.[6] In addition, the rate of chain initiation must be known and controlled, and this is done using a thermal azo initiator which decomposes at a known, constant rate to give carbon-centered radicals which react rapidly with oxygen to generate initiating peroxyl radicals.[7] The antioxidant activities represented by the absolute rate constant for inhibition, k_{inh}, are determined by measuring the oxygen uptake during the course of the inhibition period. For this purpose the integrated form of the inhibition, eq 4, is used, and the k_{inh} is obtained from a plot of the linear equation $\Delta[O_2]_t$ versus $-\ln(1-t/\tau)$ where the slope is equal to $k_p[RH]/k_{inh}$.

$$\Delta[O_2]_t = -k_p/k_{inh}[RH]\ln(1 - t/\tau) \quad (4)$$

For this method of inhibition of oxygen uptake to be useful for obtaining kinetic data, there must be appreciable oxygen uptake during the inhibition.[3a] This requires an initial free radical chain length, ν, greater than 5. In our experiments employing the less-active antioxidants (k_{inh} in the range 30–250 × 10^4 M^{-1} s^{-1}) this is readily achieved with styrene samples of 1.0–2.0 mL and the thermal initiator azobis(isobutyrylnitrile) (AIBN) concentration of approximately 0.05 M giving a rate of chain initiation (R_i) in the range 4.0 × 10^{-9} to 5.5 × 10^{-9} M s^{-1}. With more active antioxidants (k_{inh} > 250 × 10^4 M^{-1} s^{-1}), such as α-tocopherol, determined in trial exploratory runs, the procedure was modified to use 8.0 mL of styrene and a AIBN concentration of 1.00 × 10^{-2} M, resulting in chain lengths of >10 throughout the inhibition period.

The stoichiometric factor n is 2 for efficient antioxidants such as the hydroxychromans of the α-tocopherol (vitamin E) class. This factor is determined relative to α-tocopherol for other antioxidants by determination of the rate of chain initiation employing α-tocopherol under the same conditions and measuring the inhibition period for a known amount of the antioxidant where n is to be measured. Under these conditions, eq 5 is used to calculate the stoichiometric factor.

$$n = R_i\tau/[\text{inhibitor}] \quad (5)$$

The phenolic antioxidants employed gave distinct inhibitions of oxygen uptake and definite breaks in the induction periods, so that its length, τ, was readily measured. Under these conditions, eq 4 gave excellent linear plots; R^2 was at least 0.99 in all cases. Some typical plots illustrating several examples, including vitamin E for comparison, are illustrated in Figure 1.

The absolute rate constants of antioxidant activity, k_{inh}, obtained from such plots, the stoichiometric factors, n, for the series of 6-hydroxypolyalkylchromans (R_1 = CH_3), and the related derivatives of α-tocopherol (R_1 = $C_{16}H_{33}$) are summarized in Table I. It is clear that pentamethylhydroxychroman (PMHC, **1a**) in series **a** and α-tocopherol[8] in series **b** have the higher antioxidant activities as measured by k_{inh}. The k_{inh} values for the model compounds (R_1 = CH_3) are the same, within experimental error, as those for the tocopherol series (R_1 = $C_{16}H_{33}$) indicating that the phytyl side chain has no effect on

(4) (a) Ingold, K. U.; Bowry, V. W.; Stocker, R.; Walling, C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 45–49. (b) Landi, L.; Cabrini, L.; Fiorentini, D.; Stefanelli, C.; Pedulli, G. F. *Chem. Phys. Lipids* **1992**, *16*, 121–130. (c) Frei, B.; Kim, M. C.; Ames, B. N. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 4879–4883. (d) Stocker, R.; Bowry, V. W.; Frei, B. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 1646–1650. (e) Kagan, V. E.; Serbinova, E. A.; Koynova, G. M.; Kitanova, S. A.; Tyurin, V. R.; Stoytchev, T. S.; Quinn, P. J.; Packer, L. *Free Radical Biol. Med.* **1990**, *9*, 117–126. (f) Yamamoto, Y.; Komuro, E.; Niki, E. *J. Nutr. Sci. Vitaminol.* **1990**, *36*, 505–511.

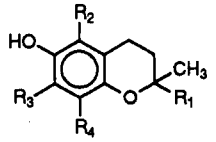
(5) Nagaoka, S.; Kuranaka, A.; Tsuboi, H.; Nagashima, U.; Mukai, K. *J. Phys. Chem.* **1992**, *96*, 2754–2761.

(6) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1965**, *43*, 2729–2736.

(7) Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095–5099.

(8) Our k_{inh} for α-tocopherol is in agreement with the literature value of 320 × 10^4 M^{-1} s^{-1} [3a] considering the experimental errors involved.

Table I. Antioxidant Activities and Stoichiometric Factors of Polyalkyl 6-Hydroxychromans and α-Tocopherol Analogs in Styrene[a] Solution at 30 °C, Thermally Initiated by AIBN[b]



no.	$R_1 = CH_3$ series[c]	$10^6 k_{inh}$ (M^{-1} s^{-1} [d])	n[e]	no.	$R_1 = C_{16}H_{33}$ series[c]	$10^6 k_{inh}$ (M^{-1} s^{-1} [d])	n[e]
1a	R_2–$R_4 = CH_3$	(3.8)[3a]	–	**1b**	–	2.9 (α-toc)	(2.0)[3a]
2a	$R_2 = R_3 = C_2H_5$, $R_4 = CH_3$	2.1	2.1	**2b**	–	2.1	1.9
3a	$R_2 = R_3 = C_2H_5$, $R_4 = H$	1.6	2.0	**3b**	–	1.5	1.7
4a	$R_2 = R_3 = (CH_3)_2CH$, $R_4 = CH_3$	0.88	1.6	**4b**	–	1.0	1.6
5a	$R_2 = R_3 = (CH_3)_2CH$, $R_4 = H$	1.1	1.9	**5b**	–	1.1	2.0
6a	$R_2 = CH_3$, $R_3 = (CH_3)_3C$, $R_4 = H$	1.9	–	**6b**	–	1.7	1.7
7a	$R_2 = (CH_3)_2CH$, $R_3 = (CH_3)_3C$, $R_4 = H$	0.46	–	**7b**	–	0.59	1.6
				8b	R_2–$R_4 = H$ (tocol)	0.51	2.0

[a] Reactions were carried out in 2.0 mL of styrene; except 8.0 mL was used for **1b**. [b] Azobis(isobutyrynitrile). Amounts used were in the range 8.0–10 × 10^{-5} mol, giving a rate of chain initiation, R_i, of 4.0 × 10^{-9}–5.5 × 10^{-9} M s^{-1}. [c] Amounts of inhibitors used were 6.3 × 10^{-9} to 10.0 × 10^{-9} mol throughout. The chain length was at least 10 for the initial part of the inhibition period and in most runs ranged >30 to 100 during inhibition. [d] The k_{inh} values calculated from plots of oxygen uptake during inhibition versus $-\ln(1 - t/\tau)$, where the slopes = $k_p[RH]/k_{inh}$ and k_p = 41 M s^{-1}.[6] Values were averaged from at least three experiments where the spread <±20%. [e] The stoichiometric factor relative to 2.0 for α-tocopherol, calculated using $n = R_i \times \tau/[\text{inhibitor}]$ where τ is the inhibition period.

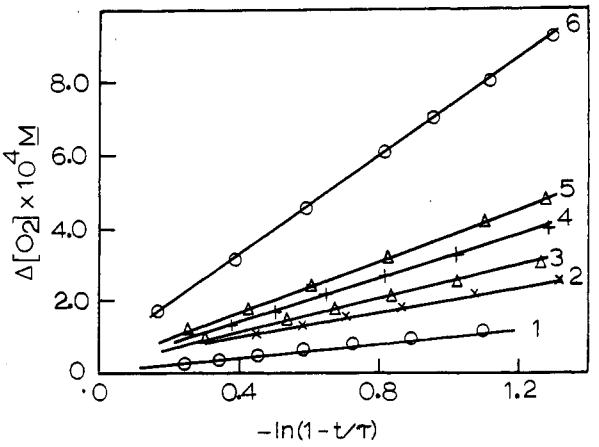
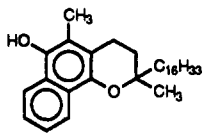
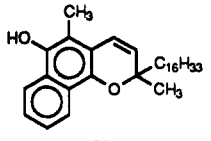
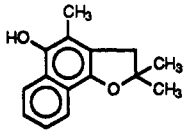


Figure 1. Plots of oxygen uptake during inhibition periods versus $-\ln(1 - t/\tau)$ for antioxidant action during AIBN initiated peroxidation of styrene. 1: α-Tocopherol, 6.73 × 10^{-9} mol; styrene, 6.78 × 10^{-2} mol; AIBN, 8.0 × 10^{-3} mol; k_{inh} = 328 × 10^4 M^{-1} s^{-1}. 2: 2,2,5-Trimethyl-7-*tert*-butyl-6-hydroxychroman (**6a**), 7.02 × 10^{-9} mol; styrene, 1.57 × 10^{-2} mol; AIBN, 8.0 × 10^{-5} mol; k_{inh} = 192 × 10^4 M^{-1} s^{-1}. 3: 2,3,6-Trimethyl-4-methoxyphenol (**10b**), 6.92 × 10^{-9} mol; styrene, 1.57 × 10^{-2} mol; AIBN, 8.00 × 10^{-5} mol; k_{inh} = 133 × 10^4 M^{-1} s^{-1}. 4: 2,2-Dimethyl-5,7-diisopropyl-6-hydroxychroman (**5a**), 7.00 × 10^{-9} mol; styrene, 1.57 × 10^{-2} mol; AIBN, 7.99 × 10^{-5} mol; k_{inh} = 105 × 10^4 M^{-1} s^{-1}. 5: 2,2,4-Trimethyl-5,7-diisopropyl-6-hydroxychroman (**4a**), 9.50 × 10^{-9} mol; styrene, 1.57 × 10^{-2} mol; AIBN, 7.99 × 10^{-5} mol; k_{inh} = 87 × 10^4 M^{-1} s^{-1}. 6: 2,2-Dimethyl-5-isopropyl-7-*tert*-butyl-6-hydroxychroman (**7a**), 9.57 × 10^{-9} mol; styrene, 1.57 × 10^{-2} mol; AIBN, 7.99 × 10^{-5} mol; k_{inh} = 44 × 10^4 M^{-1} s^{-1}.

antioxidant activity at least in homogeneous solution. The values for the other compounds vary considerably due to a combination of differential electronic and steric effects as a result of the variation of alkyl substituents on the aromatic ring.

The antioxidant activities and stoichiometric factors for the selected α-naphthol derivatives are given in Table II. Incorporation of a second fused aromatic ring causes a *remarkable increase in antioxidant activities*. Both the benzochroman **9a** and benzochromene **9b** exhibit k_{inh} values 4 times that of α-tocopherol. It is of interest to find that the conjugated double bond in **9b** has little effect on the antioxidant activity; there is only a 10% reduction in the k_{inh} compared to **9a**. This indicates, as might be

Table II. Antioxidant Activities and Stoichiometric Factors of Some α-Naphthol Derivatiyes in Styrene[a] Solution at 30 °C, Thermally Initiated by AIBN[b]

compound[c]	$10^6 k_{inh}$ (M^{-1} s^{-1} [d])	n[e]
 **9a**	11.4	1.5
 **9b**	10.2	1.4
 **9c**	28.7	1.6

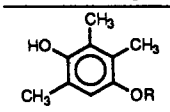
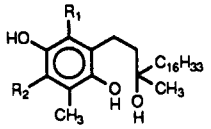
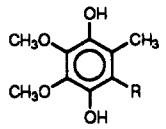
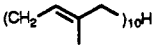
[a] A volume of 8.00 mL of styrene was used in these experiments. [b] Each run used 8.0 × 10^{-5} mol of AIBN, the R_i values were in the range 8.3 × 10^{-10} to 9.9 × 10^{-10} M s^{-1}. [c] Amounts of inhibitors **9a**, **9b**, and **9c** were 17.7, 14.1, and 6.44 nmol, respectively, and the respective chain lengths during inhibition were 16–36, 17–51, and 15–29. [d] See Table I, footnote *d*. [e] See Table I, footnote *e*.

anticipated, that the second aromatic ring exerts the predominant effect attributed to enhanced electron delocalization and stabilization of the phenolic radical in the rate-determining step of antioxidant action.

It was of special interest to design an antioxidant which possesses both the second aromatic ring and the ether oxygen *para* to the hydroxyl incorporated in a *five-membered ring* as achieved in compound **9c**. This compound possesses truly remarkable antioxidant activity. The five-membered ring raises the k_{inh} value another 2.5 times over that of compound **9a**, and overall its antioxidant activity is 10 times that of α-tocopherol in homogeneous solution.

Finally, we report on the antioxidant activities of some important hydroquinone derivatives as outlined in Table III. The hydroquinones typically gave relatively low stoichiometric factors (*vide infra*). Therefore, we deter-

Table III. Antioxidant Activities of Selected Derivatives of Hydroquinone and 2,3,5-Trimethy-4-methoxyphenol in Styrene Solution[a] at 30 °C, Thermally Initiated by AIBN[b]

compound[c]	$10^6 k_{inh}$ (M^{-1} s^{-1} [d])	n[e]
		
10a R = H	1.4*	>0.50
10b R = CH_3	1.3	2.0
		
11a R = R_2 = $CH_3\alpha$	1.5	>0.50
11b R = CH_3, R_2 = Hβ	1.1	0.64
11c R = H, R_2 = $CH_3\gamma$	0.80	>0.50
		
12a R = H (ubiquinol – 0)		
12b R =  (ubiquinol – 10)	0.31 0.35	1.9 1.0

[a] Experiments with **10a,b** and **11a,b** used 2.0 mL of styrene. The others used 1.0 mL of styrene diluted to 2.0 mL with chlorobenzene. [b] Each run used 8.0×10^{-5} mol of initiator and the rate of chain initiation was in the range 4.0 to 5.3×10^{-9} M s^{-1}. [c] Amounts of inhibitors (moles $\times 10^{-8}$) were **10a**, 2.28; **10b**, 1.04; **11a**, 11.7; **11b**, 16.2; **11c**, 4.83; **12a**, 43.4; **12b**, 53.2. The initial chain length during inhibition was at least 10, except in **11a**, the range was 5–11. [d] See Table I, footnote *d*. Results of at least six experiments were averaged. [e] See Table I, footnote *e*. Values of $n > 0.5$ have large associated errors due to oxidation of the inhibitor (see text).

mined the k_{inh} of 2,3,6-trimethyl-4-methoxyphenol (**10a**)[9] to compare with the corresponding hydroquinone **10b**. The latter gave about the same k_{inh} despite a low n value. The antioxidant activities of the tocopherol hydroquinones (**11a–c**) are all lower than the known values for the corresponding tocopherols (see Table I, **1b** and ref 3a).

The ubiquinols **12a,b** have significantly lower antioxidant activities than the other hydroquinones studied (Table III). These results are in general agreement with reports showing that the relative k_{inh} of ubiquinol-10 was 10 times less than α-tocopherol during peroxidation of methyl linoleate in hexane[4f] and 0.34–0.39 times as reactive as α-tocopherol during autoxidation of egg phosphatidylcholine in organic solvents.[4b] However, in the latter case formation of reverse micelles complicated the system compared to homogeneous solutions.

Discussion

Results on the antioxidant activities of the polyalkyl 6-hydroxychromans and α-tocopherol analogs (Table I) demonstrate the important role of steric hindrance of the phenolic hydroxyl group on the activity of both series. As pointed out earlier,[10] *ortho* substituents on alkylphenols exert two opposing effects on the k_{inh}, an accelerating effect due to electron release from the substituent and a retarding effect due to steric factors. In the tocopherol series, the accelerating effect is most pronounced on the k_{inh} of α-tocopherol which possesses 6 times the activity of the unsubstituted tocol compound (Table I, **1b** and **8b**). However, even more bulky *o*-alkyl groups such as ethyl cause a significant lowering in antioxidant activity. When the phenolic hydroxyl is flanked by *tert*-butyl and isopropyl groups (**7a**), the k_{inh} drops by almost 1 order of magnitude. A space-filling model of this system indicates that the phenolic hydroxyl is restricted from rotating and appears to prefer a nonplanar conformation with the aromatic ring. In this situation, the peroxyl radical may be forced to approach at right angles to the aromatic ring in order to abstract the phenolic hydrogen.

The antioxidant activities of both series **a** and **b** (Table I) in homogeneous solution are in marked contrast to results in aqueous micelles[11,12] and phospholipid bilayers.[13] In these heterogeneous model membrane systems, remarkable leveling and decrease of antioxidant activities were observed. These effects were attributed to hydrogen bonding by water which would tie up the lone pair on a *para* ether oxygen and thus inhibit the "steroelectronic effect" which raises antioxidant activity in homogeneous solution. In addition it was proposed that hydrogen bonding at the phenolic hydroxyl group inhibits facile transfer of the phenolic hydrogen to trap peroxyl radicals.[12,13] The latter steric effect appears to be particularly significant. Bulky alkyls *ortho* to the phenolic hydroxyl lower the k_{inh} in nonprotic homogeneous solution; however, steric hindrance to hydrogen bonding at this position "frees" this hydroxyl to trap peroxyls so that compounds like **5a** and **6a** are actually superior to α-tocopherol as antioxidants in model membranes.[13] Clearly, the reaction medium is very important when assessing antioxidant activities.

The results found for antioxidant activities of the α-naphthol series (Table II) are of particular interest in that they illustrate how structures can be designed to optimize the favorable electronic effects and raise the absolute rate constant, k_{inh}, of antioxidant action. Both the second aromatic ring and *para* ether oxygen held in a fused ring system would contribute to delocalization of the unpaired electron. These two electronic effects are optimized in compound **9c** which possesses the highest known antioxidant action in solution. It is anticipated that such compounds will also be effective antioxidants in membrane systems.

It is of interest to note that the polyalkylhydroquinones (Table III, **10**, **11**), including the tocopherol analogs, exhibit lower antioxidant activities than their cyclic chromanol analogs. This shows again that the *para* ether oxygen should be located in a fused ring system to optimize the stereoelectronic effect on stabilization of the incipient phenoxyl radical.

The antioxidant activities of the ubiquinols (**12a,b**) in solution are of particular interest in view of their significant behavior as antioxidants in natural systems.[4] The lower k_{inh} observed here accounts for the lower relative antioxidant activity reported earlier in solution.[4b,f] The two adjacent methoxyl groups appear to depress the antioxidant activity relative to the polyalkylhydroquinones (Table III, **10**, **11**). We suggest that the two adjacent

(9) Our k_{inh} value for **10a** is in good agreement with the literature value of 130×10^4 M^{-1} s^{-1}.[3a]

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methoxy groups are forced out-of-plane so that their main effect is the inductive electron withdrawal by oxygen, and as a result the developing phenoxyl radical is destabilized. This suggestion has support in the reported electrochemistry of the ubiquinones where the two adjacent methoxyls raised the reduction potentials compared to the 2,5- and 2,6-dimethoxy isomers apparently due to steric effects between the adjacent methoxys in the ubiquinones.[14]

Remarkably different results have been reported for the antioxidant activity of ubiquinol-10 in model biological systems compared to that in solution, and these effects have been reviewed.[4a] It appears to be as effective as α-tocopherol against peroxidative attack on liposomal membranes[4c,f] but *more efficient* than α-tocopherol to protect human low-density lipoprotein (LDL).[4] Such differences in the action of ubiquinol have recently been interpreted in terms of different particle sizes of the microenvironment whereby in small LDL particles the ubiquinol may function through the semiquinone radical $Q_{10}H^{\cdot}$ to "export radicals" (e.g. $HOO^{\cdot}$) from the small particle into the aqueous phase. This phenomenon is expected to be controlled by the volume of the environment available to this antioxidant. We speculate that the antioxidant activity of ubiquinols depends on the system used and would vary accordingly as follows: LDL > liposomes > homogeneous solution.

The overall efficiency of an antioxidant is determined by the number of radicals trapped per molecule, the stoichiometric factor, n, as well as the inhibition rate constant. Various factors may result in nonintegral values for n. For example, n factors greater than the "expected" 2 can arise for less-active inhibitors if self-termination of the peroxyls is significant,[15] so that the inhibition period becomes longer than implied by eqs 1 and 2. Stoichiometric factors for most phenols are usually 2. The n factors for the chromanols and derivatives (Tables I and II) vary between 1.5 and 2.0, and the lower values are probably due to ArO "wasting" reactions that result from chain-transfer reactions with the substrate and self-reaction.[3c] Values of n for derivatives of the hydroquinones were frequently found to even drop below 0.5, and in this case large errors are involved in their determination. This is undoubtedly due to the ease of oxidation in solution of most of these hydroquinones quinones.[16]

Experimental Section

Materials. Pentamethylhydroxychroman (**1a**) and 2,3,6-trimethyl-4-methoxyphenol (**10b**) were gifts from Dr. Graham Burton.[3a] α-Tocopherol was obtained from Eastman-Kodak. The preparations and sources of the polyalkyl-6-hydroxychromans (**2a–7a**) and α-tocopherol analogs (**2b–8b**) are given in refs 17 and 18 and the α-naphthol derivatives (**9a** and **9b**) in ref 19. The tocopherol hydroquinones (**11a–c**) and the ubiquinols (**12a,b**) were prepared by reduction of the commercially available hydroquinones by known procedures.[18] All antioxidants were stored at −30 °C and solutions of known concentration in chlorobenzene or hexane were prepared immediately before use. Styrene was the purest grade from Aldrich, and *tert*-butylcatechol inhibitor was removed immediately before use by an alumina adsorption column supplied with the sample.

2,3-Dihydro-5-hydroxy-2,4,4-trimethylnaphtho[1,2-*b*]furan (9c). A mixture of 2-methyl-1,4-naphthohydroquinone (5.4 g, 0.033 mol) and 2-methyl-2-propen-1-ol (3.5 g, 0.049 mol) in dioxane was refluxed for 7 h. Anhydrous $SnCl_2$ (5.0 g) and concd HCl (2.5 mL) were added, and this mixture was refluxed overnight. The reaction mixture was poured onto ice and extracted with ethyl ether, and the ether layer was washed with 5% $NaHCO_3$ and with water and dried over anhydrous Na_2SO_4. The ether was evaporated, and the product was recrystallized from petroleum ether to give colorless needles: mp 135–137 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.54 (s, 6H, 2-CH_3), 2.27 (s, 3H, 4-CH_3), 3.08 (s, 2H, 3-CH_2), 4.55 (s, 1H, 5-OH), 7.34 (s, 2H, aromatic H), and 7.89 (s, 2H, aromatic H); UV spectrum (ethanol) λ_{max} = 248 nm (log ϵ = 4.60), λ_{max} = 3.41 nm (log ϵ = 3.83). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07. Found: C, 78.88, H, 7.09. Mass spectrum, M^+ base peak m/e = 228, calcd 228.

Autoxidation Procedure. Autoxidations were carried at 30 °C at 760 torr under oxygen in a dual-channel stainless steel apparatus that has been described in detail elsewhere[21] and which was fitted with a sensitive pressure transducer for measuring oxygen uptake during inhibition periods.[11] In order to measure relatively small amounts of oxygen uptake during inhibition periods, the system was first "conditioned" at 30 °C with styrene samples in both channels of the system. A known amount of initiator was injected into the sample side, and after a steady uptake of oxygen was reached, a known amount of inhibitor in chlorobenzene was added and the oxygen uptake measured until the rate returned to the uninhibited rate. For the more reactive inhibitors, the inhibitor must be added to the styrene in the reference channel, so as to prevent oxygen uptake due to self-initiation. This was the procedure for all runs where kinetic results are reported.

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