Antioxidant Activity of 1-Thio-α-tocopherol and Related Compounds. EPR, ENDOR, and UV-Visible Absorption Spectra of Some of the Derived Phenoxyl Radicals[1]

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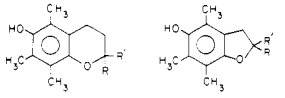
The inhibition of the azobis(isobutyronitrile) thermally initiated autoxidation of styrene at 30 °C by 1-thio-α-tocopherol and related 6-hydroxythiochromans has shown that these compounds trap fewer than 2.0 peroxyl radicals per molecule (between 1.0 and 1.8) and that they are only slightly less reactive toward peroxyl radicals than structurally related 6-hydroxychromans. A number of thiochromanoxyl radicals were generated photolytically, and their EPR and ENDOR spectra were recorded. The ENDOR cavity is unique in that it allows photolysis of the sample, and this represents the first report on the ENDOR spectra of transient radicals that must be continuously generated by photolysis. The hyperfine splittings for thiochromanoxyls are similar to those of chromanoxyl radicals, but their g values are higher by 0.0008. The UV-visible absorption spectrum of the thiotocopheroxyl radical has a band maximum at 488 nm, well above the 413 nm of α-tocopheroxyl. An addendum reports that 5-hydroxy-2,4,6,7-tetramethylbenzofuran is only ca. 10% as active toward peroxyl radicals at 30 °C as structurally related 2,3-dihydro-5-hydroxybenzofurans, the latter being a class of phenols which we have previously shown to be the most active in trapping peroxyl radicals.[5,6] An improved synthesis of 1-thio-α-tocopherol and a correction to earlier reports regarding purported syntheses of this compound are also included.

In earlier publications,[3-6] we have shown that α-tocopherol (vitamin E, **1a**) is one of the most active peroxyl radical trapping phenolic antioxidants known: k_1(**1a**) = 3.2×10^6 M^{-1} s^{-1} at 30 °C.[5,6] The high reactivity of **1a** (and

$$ROO^{\bullet} + ArOH \rightarrow ROOH + ArO^{\bullet} \quad (1)$$

R = poly(peroxystyryl)

of related 6-hydroxychromans such as **1b**, for which k_1 = 3.8×10^6 M^{-1} s^{-1}) was attributed largely to favorable stereoelectronic factors which arise because the oxygen atom in the heterocyclic ring is held in such a manner that its p type lone pair of electrons is favorably oriented so as to stabilize the tocopheroxyl radical that is produced in reaction 1.[3-6] Confirmation of the stereoelectronic



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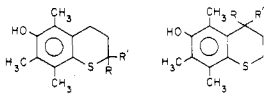
for all structures: **a**, R = CH_3, R′ = $C_{16}H_{33}$ (phytyl); **b**, R = R′ = CH_3; **c**, R = CH_3, R′ = H; **d**, R = R′ = H; **e**, R = CH_3, R′ = $COOCH_3$

arguments was obtained by synthesizing structurally related 2,3-dihydro-5-hydroxybenzofurans, such as **2a** and **2b**. These compounds were found to be even better peroxyl radical trapping agents than α-tocopherol (e.g.,[6] k_1(**2b**) = 5.7×10^6 M^{-1} s^{-1} at 30 °C), a result that was interpreted in terms of improved orbital overlap between the lone pair on the 1-oxygen and the SOMO of the derived phenoxyl radical, i.e., in terms of improved stabilization of $ArO^{\bullet}$.

Sulfur is generally considered to be more effective than oxygen at stabilizing a neighboring radical center.[7] The possibility therefore existed that 1-thio-α-tocopherol, **3a**, and related 6-hydroxythiochromans such as **3b** might be better peroxyl radical trapping agents than the corresponding chromans. The only pentamethyl-6-hydroxy-



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thiochroman we were able to isolate upon following the general procedure used to synthesize the chroman **1b** was the thiochroman **4b**, which has quite a different pattern of methyl substitution on the heterocyclic ring. Nevertheless, this compound proved to have ~87% of the peroxyl radical trapping ability of α-tocopherol,[6] i.e., k_1 (**4b**) = 2.8×10^6 M^{-1} s^{-1} at 30 °C. We were therefore encouraged to synthesize authentic analogues of **1b**, i.e., **3b** and related compounds,[8] as well as to the synthesize 1-thio-α-tocopherol, **3a**.[9] In the present paper, we compare the peroxyl radical trapping ability of several 6-hydroxythiochromans with α-tocopherol and with the corresponding 6-hydroxychromans. We also report on the EPR, ENDOR, and UV-visible spectra of the phenoxyl radicals derived from some of the 6-hydroxythiochromans. Kinetic and EPR spectroscopic data on a few other compounds have also been included. In addition, the original synthesis of **3a**[9] has been improved, as is reported in the Experimental Section. The vitamin E activity of this compound (as

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Table I. Stoichiometric Factors and Antioxidant Activities of 6-Hydroxythiochromans at 30 °C[a]

antioxidant	n (styrene)[b]	n (cumene)[b]	[antioxidant] × 10⁶, M	$\rho_0 \times 10^8$,[c] M s⁻¹	ν[d]	$nk_1 \times 10^{-6}$,[e] M⁻¹ s⁻¹
(1a)	(2.0)	(2.0)	10.7	2.0	4.5	6.4
3a	1.8	1.8	12.8	4.2	9.5	2.6
3b	1.5	1.7	11.0	4.6	10.5	2.7[f]
3c	1.2	1.6	25.3	2.8	6.4	2.0
3d	1.0	1.2	21.3	3.1	7.0	2.1[g]
3e	1.4	1.6	22.1	5.2	11.8	1.2[h]
4b	1.3[i]	1.7	11.5	2.8	6.4	4.3

[a] Mean values, SD ≤ 10% in all cases. [b] Calculated from the length of the induction period and based on n = 2.0 for **1a**. [c] Initial rate for the inhibited autoxidation of styrene under the following conditions: T = 30 °C, [styrene] = 7.64 M, [chlorobenzene] = 1.23 M, [AIBN] = 0.025 M, [antioxidant] as specified. In the absence of antioxidant, the rate of oxidation is 2.74×10^{-6} M⁻¹ s⁻¹ under these conditions and the chain length is 623. [d] Chain length for the initial portion of the inhibited autoxidation. [e] Calculated from ρ_0 via eq I taking k_2 = 41 M⁻¹ s⁻¹ and $R_i = 4.4 \times 10^{-9}$ M s⁻¹. [f] For comparison, $nk_1 = 7.6 \times 10^6$ M⁻¹ s⁻¹ for **1b**.[6] [g] For comparison, $nk_1 = 5.4 \times 10^6$ M⁻¹ s⁻¹ for **1d**. [h] For comparison, $nk_1 = 3.6 \times 10^6$ M⁻¹ s⁻¹ for **1e**. [i] A value of 1.5 was given previously.[6]

judged by a generally accepted bioassay we have previously employed to show that **2a** has more vitamin E activity than **1a**)[10] will be reported elsewhere.

Results

Measurements of Stoichiometric Factors and Antioxidant Activities. Compounds under test were used to inhibit the azobis(isobutyronitrile) (AIBN) thermally initiated autoxidation of styrene at 30 °C as described previously.[3-6,11] During the induction period, the rate of autoxidation can be represented by

$$\rho = \frac{-d[O_2]}{dt} = \frac{k_2[C_6H_5CH{=}CH_2]R_i}{nk_1[ArOH]} \qquad (I)$$

where R_i is the rate of chain initiation, the concentrations refer to the time at which the rate of oxidation is measured, k_2 is the rate constant for the reaction of the poly(peroxystyryl)peroxyl radical (ROO• in eq 2) with styrene, and n, the stoichiometric factor, is the number of chains ter-

$$ROO^\bullet + C_6H_5CH{=}CH_2 \rightarrow ROOCH_2\dot{C}HC_6H_5 \qquad (2)$$

minated per molecule of ArOH. Thus, at a known R_i (which can be readily determined by the induction period method[3-6,11-13]), the measured rate of oxidation yields the rate constant ratio k_2/nk_1. The value of k_2 has been measured as 41 M⁻¹ s⁻¹ at 30 °C.[14] The stoichiometric factor is given by

$$n = \tau R_i/[ArOH]_0 \qquad (II)$$

where τ is the duration of the induction period produced by the addition of an initial concentration of the phenolic antioxidant, $[ArOH]_0$. For the vast majority of phenolic antioxidants,[3-6,11-13,15] including α-tocopherol,[3-6,15] n has a value equal to 2.0 or close to this value. This is because the phenoxyl radical produced in reaction 1 reacts rapidly and irreversibly with a second peroxyl radical to form nonradical products which cannot continue the oxidation chain.

$$ROO^\bullet + ArO^\bullet \rightarrow \text{nonradical products} \qquad (3)$$

Some exceptions to the rule that $n \approx 2.0$ are known.[6,13] In particular, compound **4b** has previously been shown to have an n value of about 1.5 in styrene.[6] We have now discovered that all the 6-hydroxythiochromans examined have nonintegral n values that are less than 2.0 in styrene under our conditions (see Table I).

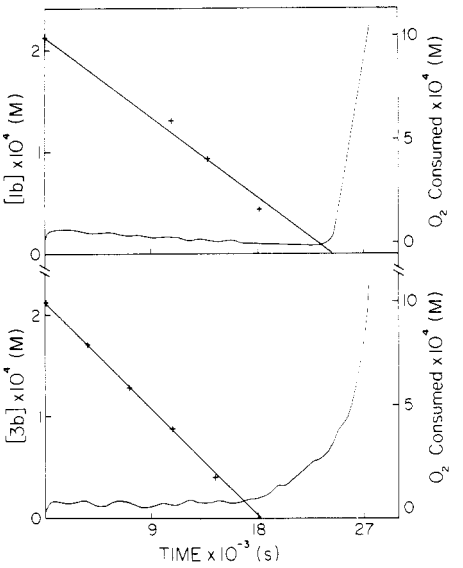

Figure 1. Oxygen consumption and HPLC-determined concentrations of **1b** (top) and **3b** (bottom) in the AIBN (0.2 M) initiated autoxidation of cumene (2 mL) in chlorobenzene (2 mL).

There are several possible reasons for n values to be less than 2.0. One of the most probable is that chain transfer via ArO•, i.e.,[16] reaction 4, competes with reaction 3. We

$$ArO^\bullet + C_6H_5CH{=}CH_2 \rightarrow ArOCH_2\dot{C}HC_6H_5 \qquad (4)$$

therefore measured n values by using cumene[17] as the oxidizable substrate. This generally gave higher n values than styrene (see Table I), which certainly suggests that some ArO• radicals may be "wasted" in styrene by chain transfer. In cumene, chain transfer may also occur (though to a lesser extent than in styrene) since the n values in cumene are still less than 2.0. Alternatively, there may be other routes by which some of the ArO• radicals are "wasted", e.g., a bimolecular self-reaction (eq 5). If the

$$ArO^\bullet + ArO^\bullet \rightarrow \text{product} \qquad (5)$$

product of this reaction is a relatively ineffective trap for peroxyl radicals, the stoichiometric factor would lie between 1.0 and 2.0, with its precise value depending on the

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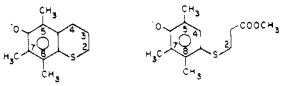
(16) This equation is not intended to imply that ArO• necessarily adds to styrene through the phenoxyl oxygen atom.
(17) Cumene gives much more sharply defined induction periods than styrene[13] because the former compound has very significantly lower chain propagation and chain termination rate constants than the latter.[14,18]

Table II. EPR Spectral Parameters for Some Sulfur-Substituted Phenoxyl Radicals[a]

parent phenol	g	a^H 2	4	5(CH_3)	7(CH_3)	8(CH_3)	ΔH_{pp}[b]
3a	2.0056		1.75 (2 H)	5.71	4.67	1.35	0.4
3b	2.0056		1.50 (2 H)	5.80	4.60	1.50	0.4
(**1b**)[c]	(2.00476)		(1.48 (2 H))	(6.04)	(4.55)	(0.96)	
3d	2.0057	2.40 (2 H)	1.50 (2 H)	5.55	4.75	1.50	0.37
4b[d]	2.0056	4.50 (1 H), 0.75 (1 H)		5.60	4.50	1.35	0.45
8b	2.0056			7.06	4.22	1.31	0.36
8c	2.0056	2.30 (1 H)		7.00	4.23	1.35	0.28
8e	2.0055	1.44 (1 H)		7.22	4.48	1.44	0.33
9c	2.0055	1.40 (1 H)	1.40 (1 H)	5.72	5.03	1.40	0.40
9d	2.0055	1.65 (2 H)	1.42 (1 H)	5.75	4.95	1.42	0.25

[a] In benzene/di-*tert*-butyl peroxide (6:1, v/v) as solvent at room temperature. Hyperfine splittings and line widths are given in gauss. The numbering for the thiochromanoxyls (**3** and **7**) and ring-open radicals (**8**) is as follows:

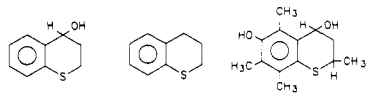


[b] Line width. [c] For comparison. Data are from ref 6. [d] In ref 6 the hfs of the H atoms in position 2 were incorrectly given as 5.5 (1 H), 0.0 (1 H). We appologize for this error. The hfs given here for this radical were obtained by simulating an EPR spectrum recorded at 6 °C, it being necessary to assume that a slow ring inversion occurred and that the rate constant for inversion was 5×10^6 s^{-1}.

balance between reactions 3 and 5 under the chosen experimental conditions.

The oxygen uptake curves for the AIBN (0.2 M) initiated autoxidation of cumene in chlorobenzene (1:1, v/v) by 2.18×10^{-4} M 2,2,5,7,8-pentamethyl-6-hydroxychroman, **1b**, and by an equal concentration of the corresponding pentamethyl-6-hydroxythiochroman, **3b**, show interesting differences near the end of the induction period (see Figure 1). The hydroxychroman (for which $n \approx 2.0$) gives a very sharp break with $\tau = 25\,200$ s. Measurements of the amount of hydroxychroman present during this time were performed by HPLC on samples taken from an identical, companion oxidation. As is also shown in Figure 1, the hydroxychroman is consumed with zero-order kinetics, as would be expected. It would appear to be completely gone at the same time as that at which a rapid oxidation rate commences. In contrast, the hydroxythiochroman only maintains the oxidation rate at an unmeasurably low value for about half as long as the hydroxychroman, i.e., for ca. 13 000 s. After this length of time, approximately one peroxyl radical will have been generated by the initiator per molecule of hydroxythiochroman. The rate of oxidation of the cumene becomes measurable after about 14 000 s and then starts to increase rapidly despite the fact that ca. 3×10^{-5} M **3b** is still present in the reaction mixture at 15 000 s [as shown by HPLC analysis on an identical companion experiment (see Figure 1)]. The oxidation rate continues to increase and reaches a value that is only slightly lower than the uninhibited rate after ca. 22 000–23 000 s.[19] The HPLC analytical results leave no doubt that the thiochroman **3b** is consumed more rapidly than the chroman **1b**. The fact that the n values obtained by measuring the length of the induction period produced by the hydroxythiochromans are lower than the n values obtained for the hydroxychromans (and most other phenols) by the same procedure is not, therefore, an artifact, i.e., it is not due to differently shaped oxidation curves. Thus, $n = 2.0$ for **1b**, whether measured from the extrapolated time it would take for complete oxidation of the phenol or from the intercept obtained by extrapolation of the rapid oxidation curve back to the time axis. In contrast, for **3b**, $n \approx 17\,600/25\,200 \times 2 = 1.4$ from the extrapolated time for complete oxidation of the phenol, while $n \approx 21\,500/25\,200 \times 2 = 1.7$ from the extrapolated rapid oxidation curve. The n values given in Table I were all obtained by the latter procedure.

Because of uncertainties in the kinetic interpretation of nonintegral stoichiometric factors as well as uncertainties in the experimental determination of n from the induction period for the 6-hydroxythiochromans, **3x**, we have elected to represent their antioxidant, peroxyl radical trapping activity as nk_1 values calculated from the measured initial rates for the inhibited autoxidation of styrene,[20] ρ_0, under standardized experimental conditions (see Table I). It should be added that compounds **5** and **6** showed no antioxidant activity in styrene nor in cumene and that compound **7** had an antioxidant activity and n value in styrene that were not significantly different from those of compound **3c**.



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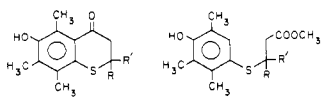
EPR Spectroscopic Properties of Thiochromanoxyl Radicals. These radicals were generated by UV photolysis of degassed solutions of the phenols in benzene/di-*tert*-butyl peroxide (6:1, v/v) at room temperature directly in the cavity of a Varian E104 EPR spectrometer. Excellent spectra were generally obtained, sufficiently intense, in fact, to prompt us to carry out ENDOR experiments in some cases (vide infra). The hyperfine splittings (hfs) that are given in Table II were derived by comparison with computer-simulated spectra. Some phenoxyls were also generated and their EPR spectra recorded from cyclic and acyclic precursors retained from the synthesis of certain **3**, viz., **8** and **9**.



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(19) Cumene oxidation rates after the induction period that are somewhat lower than the true uninhibited rate have been observed previously with a number of phenols that have $n < 2.0$.[13] There seems little doubt that in these cases some of the ArO• radicals react with one another to form a product that is a very poor antioxidant but is still capable of retarding autoxidation. Were the reactions to be followed until the rate finally returned to its uninhibited value, it is likely that extrapolation in the usual manner would yield an n value close to 2.0.

(20) The relatively high propagation rate constant for styrene[14] allows the oxidation rate to be measured during the induction period under conditions where this oxidation is a chain reaction. This is a necessary condition for the application of eq I. With cumene, a chain reaction during the induction period is not attainable, except perhaps with very ineffective chain-breaking antioxidants.

Table III. ENDOR Spectral Parameters for Some Sulfur-Substituted Phenoxyl Radicals[a]

parent phenol	T, K	a^H 2	3	4	5	7	8
3a	250		0.130	1.757	5.743	4.695	1.354
3d	200	ND[b]	ND[b]	1.555	5.500	4.568	1.296
	240	2.535	0.130	1.622	5.565	4.752	1.354
4b	220	{4.896 0.792	{0.288 0.090		5.560	4.380	1.296
	300[c]	ND[b]	0.086		5.700	4.522	1.362
8d	270	2.30	ND[b]		7.14	4.26	1.30

[a] In toluene/di-*tert*-butyl peroxide (6:1, v/v) as solvent. Hyperfine splittings are given in gauss. Position numbering begins at sulfur and goes counterclockwise in the structures as drawn (see footnote *a* in Table I). [b] Not detected, most probably because of line broadening associated with ring flip. [c] Benzene used in place of toluene.

The specific assignments of the hfs in Table II are based on the assignments previously given to comparable chromanoxyl radicals[6] and hence derive from the assignments of the α-tocopheroxyl radical due to Mukai et al.[21] Some difficulties were encountered in obtaining the hfs from the EPR spectra.[22] This is certainly due partly to the greater line width of the sulfur-substituted phenoxyl radicals relative to comparable phenoxyl radicals containing an oxygen atom para to the radical center.

Determination of Hyperfine Splittings of Thiochromanoxyl Radicals by ENDOR Spectroscopy. Some representative thiochromanoxyl radicals were studied in an ENDOR (electron nuclear double resonance) spectrometer uniquely modified for direct photolysis of samples in the cavity. The radicals were generated by continuous UV photolysis of degassed solutions of the phenols in toluene/di-*tert*-butyl peroxide (6:1, v/v) directly in the cavity of the modified Bruker spectrometer. Hyperfine splittings are given in Table III.

The agreement between the ENDOR hfs and the hfs used to fit the EPR spectra is very satisfactory as has been shown previously by Mukai et al.[21] for the chromanoxyl radicals derived from **1a**[23] and **1b**.

Kinetics of the *tert*-Butoxyl/α-Thiotocopherol Reaction and UV-Visible Spectrum of α-Thiotocopheroxyl. Laser flash photolysis (Molectron UV-24 nitrogen laser, 337 nm, ~8 ns, up to 10 mJ/pulse) of a degassed solution of **3a** in benzene/di-*tert*-butyl peroxide (3:1, v/v) at room temperature yielded the absorption spectrum shown in Figure 2 (bottom), which we assign to the α-thiotocopheroxyl radical. The absorption spectrum of α-tocopheroxyl obtained in the same way is shown for comparison in Figure 2 (top).

By monitoring of the rate of growth of the α-thiotocopheroxyl radical after the laser flash and use of a range of thiotocopherol concentrations, it is relatively straightforward to determine the rate constant for attack of the *tert*-butoxyl radical on the phenol, k_6 (reaction 6). For

$$(CH_3)_3CO^\bullet + ArOH \rightarrow (CH_3)_3COH + ArO^\bullet \quad (6)$$

α-thiotocopherol under the conditions described above, k_6(**3a**) = (3.0 ± 0.3) × 10^9 M^{-1} s^{-1}. For comparison, the analogous rate constant with α-tocopherol, which had also been determined in this laboratory under similar conditions,[24] has a value of (3.8 ± 0.5) × 10^9 M^{-1} s^{-1}.

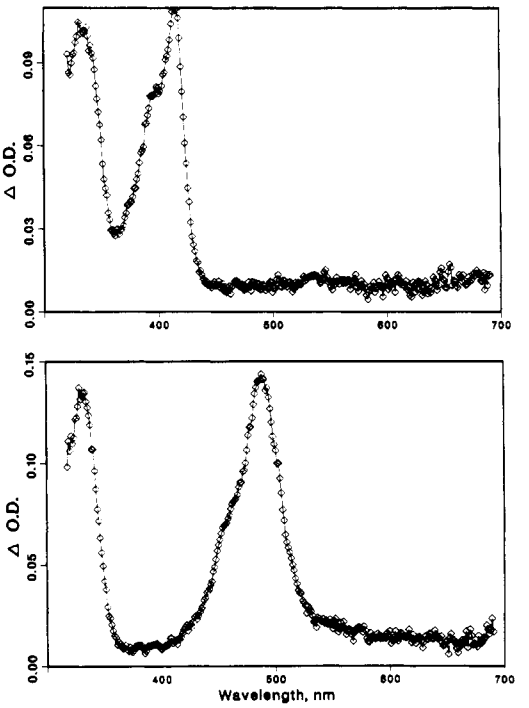


Figure 2. The UV-visible spectra of α-tocopheroxyl (top) and α-thiotocopheroxyl (bottom) radicals. The spectra were obtained 1 μs after the 337-nm laser flash photolysis of 3.7 × 10^{-3} M α-tocopherol and 2.8 × 10^{-3} α-thiotocopherol solutions in di-*tert*-butyl peroxide/benzene, 1:3 (v/v).

Discussion

1-Thio-α-tocopherol is somewhat less reactive toward peroxyl radicals than α-tocopherol, as can be seen from their respective nk_1 values of 6.4 × 10^6 M^{-1} s^{-1} and 2.6 × 10^6 M^{-1} s^{-1} (Table I). The other 6-hydroxythiochromans are also somewhat less reactive toward peroxyl radicals than the structurally related 6-hydroxychromans (see nk_1 values given for **1b,d,e** in footnotes to Table I). The ratios of nk_1 values for corresponding hydroxychromans and hydroxythiochromans, i.e., nk_1(**1x**)/nk_1(**3x**), range from 2.5 (**x** = **a**) to 3.0 (**x** = **e**). The lower reactivities of the thiochroman antioxidants relative to the chroman antioxidants can be attributed both to their smaller *n* values and their smaller k_1 values. That the sulfur-containing compounds are generally less reactive toward oxygen-centered radicals is also indicated by the rate constants found for the reaction with *tert*-butoxyl radicals, viz., k_6(**1a**) = 3.8 × 10^9 M^{-1} s^{-1} and k_6(**3a**) = 3.0 × 10^9 M^{-1} s^{-1}.

The EPR parameters of the thiochromanoxyl radicals, **3x**• (see Table II), differ only in minor ways from those of comparable chromanoxyl radicals, **1x**•[6] (see also data

(21) Mukai, K.; Tsuzuki, N.; Ishizu, K.; Ouchi, S.; Fukuzawa, K. *Chem. Phys. Lipids* **1981**, *29*, 129–135.

(22) Despite obtaining an excellent EPR spectrum with **3c**, we have not yet succeeded in assigning hfs. We had no remaining material on which to carry out an ENDOR study.

(23) We also ran the ENDOR spectrum of α-tocopheroxyl, but we obtained results that differed significantly from those of Mukai et al.[21] These workers gave ENDOR hfs of 0.098, 0.988, 1.497, 4.551, and 6.095 G at −30 °C in *tert*-butylbenzene. We obtained 0.115, 0.786, 1.267, 4.349, and 5.904 G at −33 °C in toluene. We do not understand the reason for this discrepancy.

(24) Evans, C., unpublished results in benzene/di-*tert*-butyl peroxide (1:1, v/v).

for the radical from **1b** given in Table II for comparative purposes). The g values for all the sulfur-containing radicals are higher (by ca. 0.0008) as expected.[25] The hfs for **3x•** for hydrogen atoms that are fairly remote from the sulfur (at positions 4, 5, and 7) are very similar to those for **1x•** radicals. However, the hfs at position 8 are significantly lower for **3x•** than for **1x•**, possibly because of a "through-space" interaction between the sulfur atom and the 8-methyl group in which the spin reaching this methyl group is of opposite sign to that of spin reaching this methyl group in a more or less direct fashion via the aromatic ring.

The phenoxyl radical derived from **4b** has two inequivalent but slowly interconverting hydrogen atoms at position 2 in its EPR spectrum at 6 °C (Table II) and has two inequivalent hydrogen atoms in both position 2 and position 3 in its ENDOR spectrum at 220 K but not at 300 K (Table III). This indicates that the heterocyclic ring is nonplanar (as has already been confirmed by an X-ray crystallographic study of **4b**).[6] Ring flip is probably slower for this radical than for the radical derived from **3d** which lacks the two methyl groups at position 4. For the **3d**-derived radical, the hydrogen atoms at position 2 (Tables II and III) and at position 3 (Table III) are equivalent at room temperature and at 240 K. However, the signals due to these two pairs of hydrogen atoms have broadened at 200 K (Table III) so as to become undetectable. This indicates that ring flip is starting to "freeze out" at the lower temperature. The two methyl groups in **4b** probably have a fairly profound "stiffening" effect on the heterocyclic ring flip. [In this connection, it is worth noting that in Mukai et al.s[21] ENDOR study of the radicals derived from **1a** and **1b** the pairs of hydrogen atoms at positions 3 (and 4) were still magnetically equivalent at 243 K.] Comparison of the magnitude of the hfs for the hydrogen atoms at position 2 when they are nonequivalent [e.g., **4b•**, 4.50 and 0.75 G (Table II), 4.896 and 0.792 G (Table III)] with the magnitude of the hfs for similar radicals for which the hydrogen atoms at this position are magnetically equivalent [e.g., **3d•**, 2.40 G (Table II), 2.535 G (Table III); **8d•**, 2.30 G (Table III)] suggests that these two hydrogen atoms have hfs with the same sign. However, comparison of the magnitude of the hfs at position 3 for the radical from **4b** when they are nonequivalent [at 220 K, 0.288 and 0.090 G (Table III)] and equivalent [at 300 K, 0.086 G (Table III)] indicates that these hydrogens have hfs with opposite signs [viz., $(0.288 + 0.090)/2 = 0.189$ G; $(0.288-0.090)/2 = 0.099$ G].

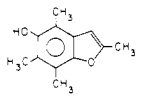
The most striking change in the EPR spectrum of radicals containing a carbonyl group at position 4 (**8x•**) compared with the **3x•** radicals is the increase in the hfs of the hydrogen atoms on the adjacent 5-methyl group. The ring-opened radicals, **9c•** and **9d•**, have hfs similar to those of thiochromanoxyls such as **3b•** and **3d•**.

The hfs measured by ENDOR spectroscopy (Table III) are in good agreement with those measured by EPR spectroscopy (Table II) and require no further comment.

The majority of phenoxyl radicals have UV–visible absorption maxima in the range 392 nm (4-fluorophenoxyl) to 412 nm (4-chlorophenoxyl).[26] This absorption does shift to longer wavelengths for 4-substituted phenoxyl radicals containing groups such as CN (443 nm) and C_6H_5 (502 nm) and heavy atoms such as Br (421 nm) and I (463 nm).[26] Nevertheless, the rather dramatic shift in the position of the absorption maximum along the series 4-methoxyphenoxyl (403 nm),[26] α-tocopheroxyl (413 nm), α-thiotocopheroxyl (488 nm) does suggest that this band could be a useful diagnostic aid in distinguishing between 4-alkoxyl- and 4-alkylthio-substituted phenoxyl radicals, as well as providing a convenient method for monitoring the kinetics of their formation and destruction.

Addendum

Several years ago we identified the 5-hydroxydihydrobenzofuran structure, e.g., **2a–c**, as having the optimized structure for antioxidant activity by a simple phenol.[5,6] We attributed the high antioxidant activity of these compounds to stereoelectronic factors arising from the fact that the heterocyclic ring in **2** is more nearly planar than in **1** and hence the 1-oxygen's p type lone pair of electrons in **2** is better oriented than in **1** for the stabilization of the phenoxyl radical product, ArO•. Since that time, it has been pointed out to us that the benzofuran ring system would be even "more planar" and that 5-hydroxybenzofurans such as **10** might be even better antioxidants than



10

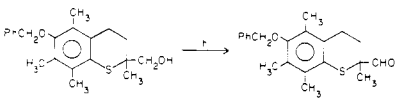
structurally comparable **2**. However, this ignores the unfavorable electronic effect that would be expected because the p type lone pair on the 1-oxygen of **10** would now be able to interact with the π electrons of the $C_2{=}C_3$ double bond [which clearly would reduce the ability of this oxygen atom to stabilize ArO• (**10•**) by conjugative electron delocalization]. We have now examined **10** and find $n \sim 2.2$ and $k_1 \approx 0.53 \times 10^6$ M^{-1} s^{-1} in styrene while, for **2c**, we have previously reported that $n \sim 2.0$ and $k_1 = 5.4 \times 10^6$ M^{-1} s^{-1}. The difference in reactivity between **10** and **2c** is dramatic but is in the expected direction.

In conclusion, we note that the peroxyl radical trapping antioxidant activities of phenols depend in complex ways on an interplay between electronic and steric factors which influence the enthalpy and entropy of reaction 1. Effective, overall antioxidant activities *also* depend on the routes available for the destruction of the ArO• radical produced in reaction 1.

Experimental Section

Materials. The 6-hydroxythiochromanol model compounds, **3b–e** and **4b**, as well as the precursors **7**, **8x**, and **9x** for some of these substances, were available from earlier synthetic work in this laboratory.[8] There was, however, insufficient 1-thio-α-tocopherol, **3a**, and so its synthesis was repeated on a much larger scale than in our earlier report.[9] Perhaps because of this scale-up certain changes were required in its synthesis as described below.

1-Thio-α-tocopherol (3a) was originally synthesized[9] from 2,3,5-trimethyl-4-hydroxybenzenethiol in 10 steps and in an overall yield of 2%. We have been forced to increase the number of steps to 11 but have achieved an overall yield of 3%. The first change involves step eight (h in ref 9), the oxidation of the alcohol **11** (**9b** in ref 9) to the aldehyde **12** (**9c** in ref 9). This step is more readily achieved by using Collins's reagent[27] than by Jones's



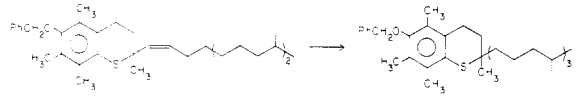
11 **12**

(25) Sulfur has a larger spin–orbit coupling constant than oxygen; see: Morton, J R.; Rowlands, J. R.; Wiffen, D. H. National Physical Laboratory (U.K.), Publ. BPR 13, 1962.

(26) Das, P. K.; Encinas, M. V.; Steenken, S.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 4162–4166.

(27) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000–4002.

method.[28] To a cooled (0 °C) mixture containing 25.8 mL of pyridine and 330 mL of methylene chloride was added CrO_3 (133 mmol, 13.0 g). The slurry was stirred for 40 min at room temperature, and thereafter, **11** (15.5 mmol, 5.3 g) was added dropwise over 4 min. Stirring was continued for 45 min at room temperature, after which a normal workup gave **12** in a yield of 4.0 g (75.4%, which is essentially identical with the 76% yield obtained previously by using Jones's method[9]). On the larger scale of the present preparation, we were unable to repeat the final step (j)[9] in the synthesis of **3a**, which involved a combined reduction and debenzylation of **13** to **3a** using H_2/Pd/C in EtOAc for 16 h at 25 °C and 1 atm pressure. In the present synthesis this procedure resulted only in the reduction of the double bond to form **14**, albeit in 100% yield. Thus, **13** (2.4 mmol, 1.3 g) in 80 mL of ethyl



13 14

acetate containing 1.3 g of 5% Pd/C was shaken under H_2 at 1 atm and room temperature for 24 h. Workup gave 2.4 mmol (1.3 g) of **14**. The debenzylation of **14** was accomplished by using iodotrimethylsilane. Thus, **14** (2.2 mmol, 1.2 g) was added to 24 mL of $CHCl_3$, cooled to 0 °C, and then treated dropwise with Me_3SiI (7.0 mmol, 1.4 g) at 0 °C for 20 min, followed by 15 min at room temperature. Workup gave **3a** (1.6 mmol, 0.71 g) in 71% yield, waxy solid, mp 36.6–36.8 °C; the acetate of **3a** is a clear colorless oil. The 500-MHz ^1H NMR spectrum of **3a** in $CDCl_3/TMS_{int}$ showed the following peaks:[29] δ 4.45 (1 H, s, O*H*), 2.78–2.73 (2 H, m, $^4CH_2$), 2.21 (3 H, s, Ar CH_3), 2.18 (3 H, s, Ar CH_3), 2.16 (3 H, s, Ar CH_3), 1.93–1.89 (2 H, m, $^3CH_2$), 1.65–1.00 (21 H, phytyl tail C*H* and CH_2) 1.34 (3 H, s, $^2CH_3$), 0.87–0.83 (12 H, phytyl tail, $HCCH_3$).

Correction. With an adequate supply of pure **3a** on hand together with improved analytical capabilities, we have reexamined the mixtures of products that are formed when 2,3,5-trimethyl-4-hydroxybenzenethiol is condensed with phytol[30] or with isophytol,[31] two reactions that have been claimed to yield **3a**. In agreement with our first study,[8] these two condensation reactions yield essentially identical mixtures which contain four major products [in order of their elution from an Ultra 1 (cross-linked methyl silicon) GC column at 250 °C, these compounds are present in relative proportions of 1.0:2.0:0.20:0.42] together with three or more minor products. None of these compounds is **3a**, and if **3a** is formed in these reactions, it is formed in a yield of <0.01%. We apologize for our earlier incorrect conclusion[8,9] that **3a** is a minor but identifiable product formed by the condensation of trimethylhydroxybenzenethiol with phytol[30] or isophytol.[31]

Other Compounds. The thiochroman-4-ol, **5**, and thiochroman-4-one were obtained from Aldrich. The latter compound was reduced by the Clemmensen–Martin method to thiochroman, **6**. To a solution of 1 g (6.09 mmol) of thiochroman-4-one in 50 mL of toluene were added 7.2 mL of H_2O and 3.6 g of Zn/Hg amalgam.[32] To the resultant mixture was added 6.3 mL of concentrated HCl dropwise, and the reaction mixture was refluxed for 15 min, after which time TLC analysis (12% ethyl acetate/hexane) showed no remaining thiochroman-4-one. The reaction mixture was cooled and filtered, the solids were washed with toluene, and the organic phase was separated, washed with brine, dried over Na_2SO_4, and evaporated in vacuo to give **6** as a colorless liquid: ^1H NMR (60 MHz, $CDCl_3$, TMS_{int}) δ 7.3–6.7 (m, 4 H, Ar *H*), 3.1–2.6 and 2.2–1.7 (multiplets, 6 H, $CH_2CH_2CH_2$). 5-Hydroxy-2,4,6,7-tetramethylbenzofuran, **10**, was available from previous work in this laboratory: mp 137.1–138.9 °C (lit.[33] mp 138–139 °C); ^1H NMR (500 MHz, $CDCl_3$, TMS_{int}) δ 6.25 (d, J = 2 Hz, 1 H, C*H*=CCH_3), 4.37 (s, 1 H, O*H*), 2.42, 2.37, 2.30, 2.23 (4 s, 12 H, 3 Ar CH_3 and $CHCCH_3$); GC/MS, m/e (relative intensity) 190 (M^+, 100), 175 (92), 145 (15), 128 (12).

Inhibition of Autoxidation. All experiments were carried out at 30.0 ± 0.2 °C. Samples containing the oxidizable substrate (styrene or cumene), azobis(isobutyronitrile) (AIBN) as a thermal initiator, and the antioxidant were vigorously shaken under 1 atm of O_2 in a sealed system. The absorption of O_2 by the sample was monitored continuously by using a pressure transducer. The equipment has been previously described in some detail.[34] Because of the high sensitivity of the system, the following procedure was employed. To the reaction flask (volume = 10 mL) was added 0.5 mL of chlorobenzene, and the system was equilibrated overnight. In the morning, 7.0 mL of styrene was injected and the flask was shaken for 30 min to 1 h. This was followed by the injection of 0.5 mL of a 0.399 M AIBN solution in chlorobenzene, and the rate of oxidation was measured in order to obtain the uninhibited rate. Then, 5 μL of a 1.71×10^{-2} M solution of α-tocopherol in chlorobenzene was injected and the oxidation was monitored. (Final concentrations were as follows: [styrene] = 7.64 M, [AIBN] = 0.025 M, [α-tocopherol] = 1.07×10^{-5} M.) When the α-tocopherol inhibited autoxidation curve had been fully recorded (i.e., from t = 0, through the induction period, and until the oxidation rate had reached, or at least approached, its uninhibited value), a 5-μL sample of the test compound at a suitable concentration in chlorobenzene was injected into the reaction flask and the new inhibited autoxidation curve was fully recorded. This procedure was repeated with the same (or a new) test compound several times during the day, with a final run being done again with α-tocopherol. Induction periods were obtained by back-extrapolation of the rapid oxidation curve (i.e., uninhibited or nearly uninhibited oxidation of styrene) following the initial, very slow, oxidation to the time axis. Stoichiometric factors were calculated from these measured induction periods and the concentration of antioxidant taking n = 2.0 for α-tocopherol. The procedure for measuring the n values in cumene (that are also given in Table I) was identical except that the reaction system contained 1.5 mL of cumene, 2.0 mL of chlorobenzene, and 0.171 M AIBN.

The two pairs of experiments, the results of which are shown in Figure 1, were carried out with 2 mL of cumene + 2 mL of chlorobenzene with an AIBN concentration of 0.2 M and an antioxidant (**1b** or **3b**) concentration of 2.18×10^{-4} M. Each of the two oxidation traces was recorded in one experiment in the usual equipment while a companion run was carried out in a vessel from which aliquots could be removed fairly readily. The quantities of antioxidant remaining during these runs were measured by HPLC [Varian 5000 equipped with a Hibar Lichrocart column 250-4 Si 60 (Merck) with UV detection at 295 nm and elution with n-hexane/*tert*-butyl methyl ether (2.4%)/2-propanol (0.05%) at 2 mL/min].

EPR spectra were recorded on a Varian E-104 EPR spectrometer. Samples of the phenols were dissolved in benzene/di-*tert*-butyl peroxide (6:1, v/v) and irradiated directly in the cavity of the spectrometer at room temperature with the light from a 1000-W high-pressure Hg lamp.

ENDOR spectra were recorded on a Bruker ER-200D-SRC electron spin resonance spectrometer interfaced to an ASPECT ER 140 data system and outfitted with a custom-constructed ENDOR cavity with a photolysis post, Bruker EN805 (SN 004). The cavity is operated in the TM_{110} mode and has two windows, 4 mm × 15 mm, parallel to the electric field. The ESR spectrum was found by applying a 1.5-kHz field modulation with a coil mounted on the pole face of the magnet. The field was locked by using the field frequency lock option. Photolysis was with light from a 75-W xenon arc (Oriel).

Laser flash photolysis was performed on apparatus that has been fully described,[26,35] as have the techniques for measuring the rate constants of radical/molecule reactions.[26,35] Transient UV–visible absorption spectra were recorded by using an optical

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multichannel analyzer equipped with a fast-gated (20 ns) image intensifier.

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Registry No. **1a**, 10191-41-0; **3a**, 85460-71-5; **3a** (radical), 114996-40-6; **3a** (acetate), 85460-72-6; **3b**, 101836-19-5; **3b** (radical), 114996-41-7; **3c**, 101836-18-4; **3d**, 101836-17-3; **3d** (radical), 114996-42-8; **3e**, 107697-39-2; **4b**, 101836-19-5; **4b** (radical), 114996-43-9; **5**, 40316-60-7; **6**, 2054-35-5; **7**, 114996-51-9; **8b** (radical), 114996-44-0; **8c** (radical), 114996-45-1; **8d**, 114996-49-5; **8e** (radical), 114996-46-2; **9c** (radical), 114996-47-3; **9d** (radical), 114996-48-4; **10**, 85979-45-9; **11**, 107697-42-7; **12**, 107697-43-8; **13**, 107697-41-6; **14**, 114996-50-8; AIBN, 78-67-1; styrene, 100-42-5; cumene, 98-82-8; 2,3,5-trimethyl-4-hydroxybenzenethiol, 85460-73-7; phytol, 150-86-7; isophytol, 505-32-8; thiochroman-4-one, 3528-17-4.

Reaction of Dilithiated Carboxylic Acids with Iodine: Evidence for the Formation of a Radical Anion Intermediate

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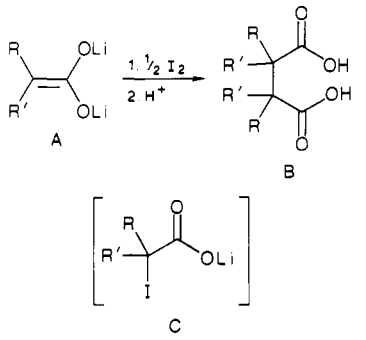
The mechanism for oxidative dimerization of carboxylic acid dianions involves single electron transfer to iodine, producing an organic anion radical. Rearrangement of this species was observed with suitable substrates at a rate competitive with intermolecular reactions. The radical anion can dimerize or react with iodine. The iodide thus generated can be isolated (reaction with excess of iodine) or can participate in a polar S_N2-type reaction sequence leading to dimeric products (reaction with $^1/_2$ equiv of iodine). The interference by free amines (liberated during the metalation with lithium amides) is rationalized by the formation of a charge-transfer complex with iodine which decomposes, liberating protons.

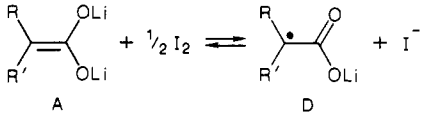
Introduction

Carboxylic acid dianions are very useful reagents in preparative organic chemistry.[1] Their highly electron-rich character renders them particularly susceptible to reactions proceeding by electron transfer. Early studies by Ivanoff[2] have shown that the dianions of carboxylic acids react with bromine to give dimeric products. Recently Belletire et al.[3] have reported a method for the synthesis of succinic acid derivatives B via oxidative coupling of a dilithiated carboxylic acid A (Scheme I). In these studies, iodine was used as the oxidant, and a route involving the formation of the iodide C, followed by a nucleophilic displacement with the dianion A, was suggested. This mechanism was proposed, for instance, for the dimerization of ester enolates induced by treatment with iodine.[4] However, the possibility that electron transfer was involved was also considered.[5] In this work we have used electrochemical techniques and the characteristic ring-opening or ring-forming reactivity of radicals to obtain further information about the mechanism of the oxidative dimerization of dilithiated carboxylic acids.

Scheme I. Preparation of Succinic Acid Derivatives



Scheme II. Electron Transfer between Dilithiated Carboxylic Acids and Iodine



Results and Discussion

Oxidation Potentials. The standard free energy for electron transfer between a carboxylic acid dianion and iodine (Scheme II) can be estimated by the difference between the oxidation potentials of the dianion and the I^-/I_2 couple. Such a simple calculation has proved to be successful, for example, in predicting whether the addition of an organic cuprate to an α,β-unsaturated carbonyl compound could proceed via an initial electron transfer.[6] A more elaborate treatment, based on Marcus theory, has been developed by Eberson for analogous electron transfers involving organic donors and acceptors.[7] In practice, this method suffers, however, from the requirement that the

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