6 H), 5.8–6.2 (m, 6 H); UV (cyclohexane) λ_{max} 255 (ϵ 24 800), 265 (33 700), and 276 (27 000).

Irradiation of Trienes. The general procedure was to prepare solutions of the particular triene in cyclohexane at concentrations on the order of 0.07–0.08 M containing a known amount of *n*-tridecane as internal standard for GLC analysis. The solutions were irradiated at various wavelengths from 300–350 nm and samples were periodically withdrawn for GLC analysis at intervals of 5 min to 1 h on a 14 ft × $^1/_8$ in. column of 10% Carbowax 20M on 80–100 mesh Chromosorb P. Ultimately, irradiations were carried out on an optical bench with 313-nm light isolated from the output of a high-intensity mercury lamp, using either a solution filter combination of 0.5% w/v potassium hydrogen phthalate in water (1 cm) 15% w/v $KCr(SO_4)_2 \cdot 12H_2O$ in 1.0 N H_2SO_4 (2 cm)[48] or a grating monochromator. Details on the distribution of trienes obtained in these irradiations are to be found in ref 42.

Irradiation of Cycloheptadienones. In a typical experiment, a solution of 42.5 mg (3.1×10^{-4} mol) of dienone **2** in 5 mL of cyclohexane was prepared, 180 μL of a 0.01 M solution of *n*-tridecane in cyclohexane was added, and the solution was purged with nitrogen and irradiated at 313 nm (see above) at 20 °C with use of a Pyrex filter. The course of reaction was monitored by GLC, using a 14 ft × $^1/_8$ in. column of 10% Carbowax 20 M on 80–100 mesh Chromosorb P at an oven temperature of 115 °C and a flow rate of 30 mL/min. The results are given in the Results section. Entirely analogously experiments were made with use of dienone **1**.

(48) Parker, C. A. "Photoluminescence in Solution"; Elsevier: New York, 1968; pp 186–190.

Acknowledgment. This study was supported in part by Grant CHE-7819750 from the National Science Foundation. We are grateful to a number of colleagues for their help and their criticisms, including Professors S. R. Wilson, W. C. Agosta, and J. A. Berson and Drs. David A. Dunn and Angelo C. Brisimitzakis. We are also grateful to two of the referees for their constructive suggestions based on a very thorough reading of the original manuscript.

Registry No. **1**, 85236-00-6; **1** (adduct with **7**), 87362-95-6; **2**, 85236-01-7; **2** (adduct with **7**), 87420-92-6; **3a**, 42104-03-0; **3b**, 36269-78-0; **4**, 29639-53-0; **5**, 87362-94-5; **7**, 4233-33-4; **8**, 14947-19-4; **9**, 2417-80-3; **10**, 14947-20-7; **11**, 15192-80-0; $HC{\equiv}CCH_2CH(OSO_2C_6H_4\text{-}p\text{-}CH_3)CH_3$, 58456-48-7; $(Z)\text{-}H_3CCH{=}CHC{\equiv}CH$, 1574-40-9; $(E)\text{-}H_3CCH{=}CHC{\equiv}CH$, 2004-69-5; $(Z)\text{-}H_3CCH{=}CHC{\equiv}CCH_2CH(OH)CH_3$, 52944-44-2; $(E)\text{-}H_3CCH{=}CHC{\equiv}CCH_2CH(OH)CH_3$, 52944-45-3; $(Z,E)\text{-}H_3CCH{=}CHCH{=}CHCH_2CH(OH)CH_3$, 52944-46-4; $(Z,Z)\text{-}H_3CCH{=}CHCH{=}CHCH_2CH(OH)CH_3$, 52944-47-5; $(Z,E)\text{-}H_3CCH(OSO_2C_6H_4\text{-}p\text{-}CH_3)CH_2CH{=}CHCH{=}CHCH_3$, 58822-86-9; $(Z,Z)\text{-}H_3CCH(OSO_2C_6H_4\text{-}p\text{-}CH_3)CH_2CH{=}CHCH{=}CHCH_3$, 58822-87-0; tropone, 539-80-0.

Supplementary Material Available: Four tables of X-ray data for the adduct of PTAD and dienone **1**, including fractional coordinants, thermal parameters, bond distances, and bond angles (4 pages). Ordering information is given on any current masthead page.

Autoxidation of Biological Molecules. 4. Maximizing the Antioxidant Activity of Phenols[1]

G. W. Burton, T. Doba,[2] E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad, and K. U. Ingold*

Contribution from the Division of Chemistry, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6. *Received April 5, 1985*

Abstract: Rate constants, k_1, for H-atom abstraction by peroxyl radicals from α-tocopherol and 35 structurally related phenols have been measured at 30 °C by the inhibited autoxidation of styrene (IAS) method. An independent laser-flash kinetic EPR method was used with ten of these phenols which gave k_1 values at 24 °C that were in satisfactory agreement with the values found by the IAS method. The structures of several phenols were determined by X-ray analysis. The EPR spectral parameters for the phenoxyl radicals derived from many of these phenols were also measured. The relative magnitudes of k_1 values for phenols that are structurally closely related and have an oxy substituent para to the hydroxyl group can be correlated with the degree of stabilization of the phenoxyl radical. Stabilization depends on two factors: (i) the extent of orbital overlap between the 2p type lone pair on the para oxygen atom and the aromatic π electron system and (ii) the electron-donating or withdrawing character of the group bonded to the para oxygen atom. Orbital overlap depends on the dihedral angle, θ, between the direction of the 2p orbital on the para oxygen and a line perpendicular to the aromatic plane. It can be estimated from the X-ray structures. Along the series 4-methoxytetramethylphenol (VIc), 6-hydroxy-2,2,5,7,8-pentamethylchromene, 6-hydroxy-2,2,5,7,8-pentamethylchroman, and 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran (IIIb), k_1 increases from 3.9×10^5, 2.5×10^6, 3.8×10^6, to 5.7×10^6 M^{-1} s^{-1}, as θ decreases from 89, 38, 17, to 6°. Compound IIIb is the most active antioxidant being 1.8 times more active than α-tocopherol. For 2-substituted 6-hydroxy-2,5,7,8-tetramethylchromans log (k_1/M^{-1} s^{-1}) can be correlated with the σ_1 constant of the 2-substituent, $\rho_1 = -1.25$. For these compounds and for some 2,6-dimethylphenols log (k_1/M^{-1} s^{-1}) can also be correlated with the extent of stabilization of the corresponding phenoxyl radicals as measured by the unpaired spin density at the two ortho methyl groups. Some additional kinetic and spectroscopic data are presented. It is also shown that the perpendicular methoxy group in VIc is not deactivating relative to a hydrogen atom but is, instead, about as activating as a methyl group.

α-Tocopherol (α-T) is not only the most biologically active component of vitamin E but, as we have previously reported,[1c,3] it is also one of the best chain-breaking, phenolic antioxidants known. That is, α-T and a number of structurally related model compounds react more rapidly with peroxyl radicals (reaction 1) than do otherwise similar phenols that lack the fused 6-membered heterocyclic ring. We have concluded[3] that stereoelectronic effects

$$ROO\cdot + ArOH \xrightarrow{k_1} ROOH + ArO\cdot \qquad (1)$$

conferred on α-T by this ring are largely responsible for the high reactivity of α-tocopherol and related compounds. The heterocyclic ring ensures that the 2p-type lone pair of electrons on the ring oxygen adopts an orientation more or less perpendicular to the plane of the aromatic ring and, in this orientation, this 2p-type lone pair stabilizes the developing phenoxyl radical.[3] The superior antioxidant behavior of α-T is further supported by our finding

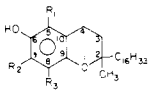
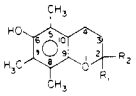
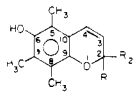
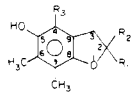
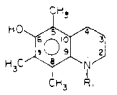
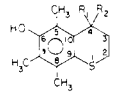
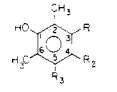
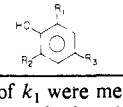
(1) (a) Issued as NRCC No. 24983. (b) Part 3: Burton, G. W.; Joyce, A.; Ingold, K. U. *Arch. Biochem. Biophys.* **1983**, *221*, 281–290. For preliminary accounts of portions of this work, see: (c) Burton, G. W.; Hughes, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 5950–5951. (d) Doba, T.; Burton, G. W.; Ingold, K. U. *Ibid.* **1983**, *105*, 6505–6506. (e) Doba, T.; Burton, G. W.; Ingold, K. U.; Matsuo, M. *J. Chem. Soc., Chem. Commun.* **1984**, 461.

(2) NRCC Research Associate 1982–1985.

(3) (a) Burton, G. W.; Le Page, Y.; Gabe, E. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 7791–7792. (b) Burton, G. W.; Ingold, K. U. *Ibid.* **1981**, *103*, 6472–6477.

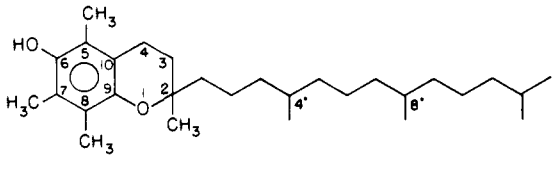
0002-7863/85/1507-7053$01.50/0 Published 1985 by the American Chemical Society

Table I. Structures, Identifying Symbols (IS), and Values of k_1 for Selected Phenolic Antioxidants[a]

structure	R_1	R_2	R_3	IS	10^4k_1 (M^{-1} s^{-1})[b] IAS	LKEPR
	H	H	CH_3	δ-T	44	33
	H	CH_3	CH_3	γ-T	140	70
	CH_3	H	CH_3	β-T	130	
	CH_3	CH_3	CH_3	α-T	320	260
	CH_3	CH_3	H	DMT	180	
	H	H		Ia	270	
	CH_3	CH_3		Ib	380	
	CH_3	C(O)OH		Ic	110	
	CH_3	C(O)OCH3		Id	180	
	CH_3	$CH_2C(O)OH$		Ie	190	
	CH_3	$CH_2C(O)OCH_3$		If	270	
	CH_3	$(CH_2)_2C(O)OH$		Ig	370	
	CH_3	$(CH_2)_2C(O)OCH_3$		Ih	330	
	CH_3	CH_2OH		Ii	270	
	CH_3	OCH_3		Ij	150	
	CH_3	CH_3		IIa	250	200
	CH_3	$CH_2C(O)OH$		IIb	100	
	H	CH_3	CH_3	IIIa	540	
	CH_3	CH_3	CH_3	IIIb	570	
	CH_3	C(O)OH	CH_3	IIIc	160	
	CH_3	CH_3	H	IIId	320	
	H			IVa		
	$C(O)CH_3$			IVb	12	
	CH_2CH_3			IVc	200	200
	CH_3	CH_3		V	280	180
	H	OCH_3	H	VIa	94	
	H	OCH_3	CH_3	VIb	130	
	CH_3	OCH_3	CH_3	VIc	39	28
	CH_3	CH_3	CH_3	VId	36	
	CH_3	CH_3	H	VIe	11	
	H	CH_3	H	VIf	8.5	
	CH_3	H	CH_3	VIg	7.5	6.9
	H	H	H	VIh	2.5	
	$(CH_3)_3C$	$(CH_3)_3C$	CH_3O	VIIa	11	11
	$(CH_3)_3C$	$(CH_3)_3C$	CH_3	VIIb	1.4	2.4
	$(CH_3)_3C$	$(CH_3)_3C$	H	VIIc	0.31	

[a] Values of k_1 were measured by the inhibited autoxidation of styrene (IAS) at 30 °C method and by the laser/kinetic EPR (LKEPR) method at 24 °C. [b] For each phenol k_1 was measured in 2–15 independent experiments. For the IAS measurements the spread in k_1 values was <±10% in every case. For the LKEPR measurements the spread was generally <±15%.

that it accounts for most, if not all, of the antioxidant activity of the lipid fraction of human blood plasma and red blood cells.[1b]



α-Tocopherol (α-T)

The following question still remains: are chain-breaking antioxidant structural features fully optimized in α-tocopherol? More specifically, is the stereoelectronic effect maximized in α-T or are there other structures that express the effect more fully? Furthermore, what other features and/or properties does α-T possess that make it the major lipid-soluble, biological chain-breaking antioxidant? We have approached these questions from the chemical, or in vitro, side by synthesizing a wide variety of phenols structurally related to α-tocopherol and have measured their absolute reactivities toward peroxyl radicals, i.e., we have measured values for k_1. For some of these compounds k_1 values have been measured by two quite independent techniques. These kinetic data have then been correlated with structural features, some of our compounds having also been examined by X-ray crystallography. Other properties of these materials have also been examined such as the EPR spectra of the corresponding phenoxyl radicals, the self-reactions of these phenoxyls, and their (non)reaction with molecular oxygen. These in vitro studies have been designed to "set the stage" for a planned series of in vivo experiments in which we will examine the vitamin E activities and biokinetic properties of certain synthetic compounds relative to those of natural (2*R*,4′*R*,8′*R*)-α-tocopherol.

Results

The phenols examined in this work are divided for convenience into the 8 classes shown in Table I. These classes are the following: the tocopherols, δ-T–α-T and 5,7-dimethyltocol, DMT; the 6-hydroxy-5,7,8-trimethylchromans, Ia–Ij; the related chromenes, IIa and IIb; the 5-hydroxy-6,7-dimethyl-2,3-dihydrobenzofurans, IIIa–IIId; the 6-hydroxy-5,7,8-trimethyl-1,2,3,4-tetrahydroquinolines, IVa–IVc; a 6-hydroxy-5,7,8-trimethyl-3,4-dihydrobenzothiopyran, V; the 2,6-dimethylphenols, VIa–VIh; and the 2,6-di-*tert*-butylphenols, VIIa–VIIc. The numbering systems used with these compounds are also shown on the structures in this table.

Measurement of k_1 Values. Inhibited Autoxidation of Styrene (IAS) Method. Absolute values of k_1 were obtained for all the

phenols listed in Table I by using them to inhibit the azobis(isobutyronitrile) (AIBN) thermally initiated autoxidation of styrene at 30 °C and measuring the rate of autoxidation during the initial portion of the induction period.[3-9] The advantages of styrene as the oxidizable substrate have been enumerated.[3b] If appropriate precautions are taken, this is by far the simplest procedure for measuring k_1 values. The IAS method is also the most versatile in terms of the range in k_1 values that can be determined, and furthermore, it is highly reliable and reproducible. To obtain good kinetic data it is essential that a sufficiently low rate of chain initiation be employed for there to be an appreciable chain length for autoxidation even at the beginning of the induction period. In addition, the apparatus must be sufficiently sensitive to measure very small rates of oxygen absorption ($\sim 1 \times 10^{-9}$ M s^{-1}) with high precision. All our measurements of k_1 by this procedure have been carried out at chain lengths >4. We have also greatly improved the sensitivity of our oxidation apparatus compared with that used in our original kinetic studies on the tocopherols[3] (see Experimental Section). Results are given in Table I. Despite its many advantages, the inhibited autoxidation of styrene method does suffer from the fact that k_1 is not itself directly measured. That is, the rate of oxidation during the induction period can be represented by

$$\frac{-d[O_2]}{dt} = \frac{k_2[C_6H_5CH{=}CH_2]R_i}{nk_1[ArOH]}$$

where R_i is the rate of chain initiation, the concentrations refer to the time at which the rate of oxidation is measured, n is the number of oxidation chains terminated per molecule of ArOH, and k_2 is the rate constant for the chain propagation step:

$$POO\cdot + C_6H_5CH{=}CH_2 \rightarrow POOCH_2\dot{C}HC_6H_5 \quad (2)$$

In this equation POO· represents the poly(peroxystyryl)peroxyl radical. Thus, at a known R_i (which can be readily determined by the induction period method[1b,3-10]), the measured rate of oxidation actually yields the rate constant ratio k_2/nk_1. The stoichiometric factor, n, has been shown to be 2.0, or very close to 2.0, for the majority of phenolic antioxidants[3-6,10-12] including, in particular, α-tocopherol[3,12] under the conditions commonly employed in kinetic experiments. The accuracy of the absolute values of k_1 that have been measured by the IAS method will therefore ultimately depend on the accuracy of the measured value for k_2 at 30 °C. We used the reported value[13] of 41 M^{-1} s^{-1} for k_2.

In 1981 we pointed out[3b] that literature values for k_1 for α-T which had been measured by such varied techniques as oxygen absorption, chemiluminescence, and pulse radiolysis covered the surprisingly wide range 2.0×10^5 to 2.3×10^7 M^{-1} s^{-1} for alkylperoxy radicals.[14] There has been only a slight improvement in this situation over the intervening years. Briefly, a chemiluminescence method has been reported[15] to yield $k_1(C_6H_5CH(CH_3)OO\cdot + \alpha\text{-T}) = 1.5 \times 10^5$ M^{-1} s^{-1} at 25 °C; a pulse radiolysis method has revised $k_1(c\text{-}C_6H_{11}OO\cdot + \alpha\text{-T})$ from 2.3×10^7 M^{-1} s^{-1} [16] down to 7.9×10^6 M^{-1} s^{-1} [17] at room temperature; and the inhibited autoxidation method with methyl linoleate as the oxidizable substrate has yielded a value of 5.1×10^5 M^{-1} s^{-1} at 37 °C.[18,19] These values should be compared with our original value[3] for $k_1(POO\cdot + \alpha\text{-T})$ of 2.4×10^6 M^{-1} s^{-1} at 30 °C and our current revised value[1c] of 3.2×10^6 M^{-1} s^{-1}. There is fairly strong evidence[21-25] to suggest that k_1 values do not to any great extent depend on the structure of the alkylperoxyl radical.[14] It therefore seemed desirable to check some of our IAS k_1 values with use of an independent technique.

Laser-Flash Kinetic EPR (LKEPR) Method. The pulse from a nitrogen laser was focussed on a sample in the cavity of an EPR spectrometer which contained di-*tert*-butyl ketone and a phenol in an oxygen-saturated hydrocarbon solvent.[24-27] Peroxyl radicals are formed in an essentially instantaneous process[28] by the reaction sequence,

$$(Me_3C)_2C{=}O \xrightarrow{h\nu} Me_3C\cdot + Me_3C\dot{C}{=}O \quad (3)$$

$$Me_3C\cdot + O_2 \rightarrow Me_3COO\cdot \quad (4)$$

$$Me_3C\dot{C}{=}O + O_2 \rightarrow Me_3CC(O)OO\cdot \quad (5)$$

By a careful choice of spectrometer settings and other experimental conditions (see Experimental Section) it was possible, for phenols less reactive than α-T, to monitor the decay of the peroxyl radical signal under conditions of (pseudo) first-order kinetics without interference from the growth of the phenoxyl radical signal. Values of k_1 for the reaction of α-T and a number of less reactive phenols with the mixture of *tert*-butylperoxyl and pivaloylperoxyl radicals formed in this system are given in Table I. They were calculated from the relation,

$$k_1 = \ln 2/n[ArOH]\tau_{1/2}$$

where $\tau_{1/2}$ is the peroxyl radical half-life. It was assumed that $n = 1.0$ since any peroxyl/phenoxyl reaction should be unimportant in this system during the early stages of the peroxyl radical decay. The agreement with the results obtained by the IAS method is satisfactory considering the fact that the peroxyl radicals used in the two experiments really are quite different and in view of all the potential experimental errors and uncertainties.[14b]

For phenols that were more reactive than α-T it was necessary to work with very low concentrations of phenol in order to obtain a decay trace that did not merely reflect the time constant of the system. Sample depletion, even during a single pulse, then became a significant problem and reliable LKEPR k_1 values could not be determined.

Deuterium Kinetic Isotope Effect. Reaction 1 has been written

(4) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1962**, *40*, 1851–1864.
(5) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 1744–1751.
(6) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 2800–2806.
(7) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1964**, *42*, 1044–1056.
(8) Brownlie, I. T.; Ingold, K. U. *Can. J. Chem.* **1966**, *44*, 861–868.
(9) Brownlie, I. T.; Ingold, K. U. *Can. J. Chem.* **1967**, *45*, 2419–2425.
(10) Boozer, C. E.; Hammond, G. S.; Hamilton, C. E.; Sen, J. N. *J. Am. Chem. Soc.* **1955**, *77*, 3233–3237.
(11) Horswill, E. C.; Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1966**, *44*, 985–991.
(12) Winterle, J.; Dulin, D.; Mill, T. *J. Org. Chem.* **1984**, *49*, 491–495.
(13) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1965**, *43*, 2729–2736.
(14) (a) We specifically exclude $Cl_3COO\cdot$ and related radicals having electron-withdrawing atoms or groups attached ot the α-carbon since such species are known to be very much more reactive than alkylperoxyl radicals toward a variety of reagent. See, e.g., Packer et al. (Packer, J. E.; Slater, T. F.; Willson, R. L. *Nature (London)* **1979**, *278*, 737–738) which for $Cl_3COO\cdot + \alpha$-T gives $k_1 = 5 \times 10^8$ M^{-1} s^{-1}. See also: Packer, J. E.; Willson, R. L.; Bahnemann, D.; Asmus, K.-D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 296–299. Wolfenden, B. S.; Willson, R. L. *Ibid.* **1982**, 805–812. Mönig, J.; Asmus, K.-D.; Schaeffer, M.; Slater, T. F.; Willson, R. L. *Ibid.* **1983**, 1133–1137. (b) A referee has pointed out that $Me_3CC(O)OO\cdot$ would also be expected to be more reactive than alkylperoxyls for the same reason (see also: Zaikov, G. E.; Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1969**, *47*, 3017–3029). The LKEPR method is therefore subject to an additional uncertainty.
(15) Niki, E.; Tanimura, R.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1551–1555.
(16) Simic, M. G. *J. Chem. Educ.* **1981**, *58*, 125–131.
(17) Hunter E. P. L.; Simic, M. G. "Oxy Radicals and Their Scavenger Systems; Proceedings of the Third International Conference on Superoxide and Superoxide Dismutase"; Cohen, G., Greenwald, R. A., Eds.; Elsevier: New York, NY, 1982 (Pub. 1983); Vol. 1, pp 32–37.
(18) Niki, E.; Saito, T.; Kawakami, A.; Kamiya, Y. *J. Biol. Chem.* **1984**, *259*, 4177–4182.
(19) A value for k_1 (HOO· + α-T) of 2×10^5 M^{-1} s^{-1} in 85% acidified ethanol at room temperature has also been reported[20] However, a reduction in k_1 in hydrogen bonding solvents is to be expected.
(20) Arudi, R. L.; Sutherland, M. W.; Bielski, H. J. "Oxy Radicals and Their Scavenger Systems, Proceedings of the Third International Conference on Superoxide and Superoxide Dismutase"; Cohen, G., Greenwald, R. A., Eds.; Elsevier: New York, NY 1982 (Pub. 1983); Vol. 1, pp 26–31.
(21) Mahoney, L. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 547–555.
(22) Ingold, K. U. *Spec. Pulb. Chem. Soc.* **1971**, *No. 24*, 285–293.
(23) Howard, J. A. In "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, pp 3–62.
(24) Howard, J. A.; Furimsky, E. *Can. J. Chem.* **1973**, *51*, 3738–3745.
(25) Chenier, J. H. B.; Furimsky, E.; Howard, J. A. *Can. J. Chem.* **1974**, *52*, 3682–3688.
(26) Howard, J. A.; Tong, S. B. *Can. J. Chem.* **1980**, *58*, 1962–1965.
(27) Howard, J. A. *Rev. Chem. Intermed.* **1984**, *5*, 1–19.
(28) Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095–5099.

in the conventional manner to show a direct hydrogen atom transfer from the phenol to the peroxyl radical. Substantial deuterium kinetic isotope effects in phenol-inhibited autoxidations in nonpolar media[3-6] serve to confirm the direct H atom transfer for phenols having reactivities less than or equal to that of α-tocopherol. However, for phenols that are more reactive than α-T (for α-T we find $k_1^H/k_1^D = 5.4 \pm 0.4$) there is the possibility that reaction occurs via an initial, rate-controlling electron transfer,[29] in which case there would be no deuterium isotope effect.

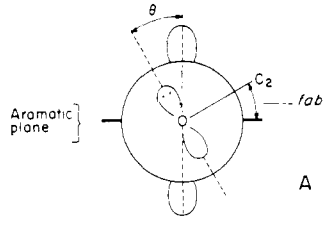
$$\mathrm{ROO\cdot} + \mathrm{ArOH} \xrightarrow[\text{controlling}]{\text{rate}} \mathrm{ROO^-} + \mathrm{ArOH^{+}\cdot} \qquad (6)$$

$$\mathrm{ArOH^{+}\cdot} \rightarrow \mathrm{ArO\cdot} + \mathrm{H^+} \xrightarrow{\mathrm{ROO^-}} \mathrm{ROOH} \qquad (7)$$

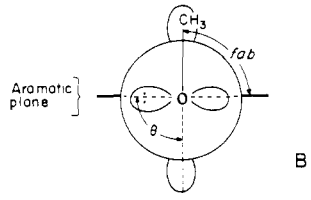
We therefore employed the IAS method to measure the deuterium isotope effect for the two most reactive phenols, IIIa ($k_1^H/k_1^D = 4.6 \pm 0.6$) and IIIb ($k_1^H/k^D = 4.4 \pm 0.4$). Since these two compounds exhibited a substantial isotope effect we conclude that H atom transfer is rate controlling in all cases.

Structures and Stereoelectronic Factors. X-ray Crystallography. The k_1 value for α-T is about eight times larger than that for 4-methoxytetramethylphenol[3] (VIc), which could serve as a model for α-T except that it lacks the fused heterocyclic ring. As was noted in the introduction, we have attributed the high reactivity of α-T to the fact that the 2p-type lone pair of electrons on the ring oxygen is constrained by the heterocyclic ring to lie approximately perpendicular to the aromatic plane. It is therefore well positioned to stabilize the incipient α-tocopheroxyl radical; this weakens the O–H bond and, in consequence, α-T has a high k_1 value. By contrast, in VIc the steric interaction between the methoxy group and the methyl groups in the 3 and 5 positions forces the methoxy group into a position perpendicular to the aromatic plane. In this position the 2p-type lone pair on the methoxyl oxygen lies in the plane of the ring. It is therefore unable to stabilize the incipient phenoxyl radical. As a consequence, VIc has a relatively strong O–H bond and a relatively small k_1 value.

These conclusions were confirmed by X-ray crystallographic analyses of the pentamethyl-6-hydroxychroman, Ib (α-T is a liquid at room temperature), and of VIc.[3a] The X-ray structure of Ib showed that the heterocyclic ring adopted a half-chair conformation with a dihedral angle *fab* (see footnote to Table II) between the aromatic ring and the O–C_2 bond of 15.9° or 19.0°.[30] This implies that the 1-oxygen's 2p-type lone pair makes a dihedral angle, θ (≡*fab*), of about 17° with respect to the axis of the 2p orbital at the adjacent aromatic carbon, see A. The analysis of



VIc showed that the methoxyl group was almost perpendicular to the ring (*fab* = 88.6°).[3a] In this molecule, therefore, θ is presumably ca. 90°, see B.



As an aid to understanding the relative magnitudes of the k_1 values found for different phenols, we undertook some additional X-ray analyses. In Table II we present torsion angles for the heterocyclic ring of Ib, Ic, IIb, IIId, and V. The complete X-ray structural data for Ic, IIb, IIId, and V are given as Supplementary Material; the data for Ib and VIc have been presented previously.[3a] Unfortunately, crystals suitable for X-ray analyses could not be grown for IIIa–c, nor for IVc and some other kinetically interesting phenols.

Table II. Summary of Torsion Angles (deg) for the Heterocyclic Ring of Various Hydroxychromans and Analogues as Determined by X-ray Diffraction Analysis[a]

angle	Ib[b]	Ib[c]	Ic[d]	Ic[e]	IIb	IIId	V
fab = θ	−15.9	−19.0	−13.7	−15.4	−37.8	−5.9	−10.8
abc	48.3	50.0	43.4	44.1	50.8	10.7	45.3
bcd	−62.7	−62.1	−60.1	−59.7	−33.3	−11.1	−67.7
cde	44.2	42.8	46.5	45.3	1.4		45.5
def (*cdf*) = γ	−11.2	−11.5	−17.1	−17.1	−15.6	(8.1)	−5.3
efa (*dfa*)	3.9	1.4	−0.3	1.2	3.0	(−1.8)	6.9

[a] Ring parameter designations are

for structures I, II, and V;

for structure III. [b] Molecule 1 of unit cell (ref 3a). [c] Molecule 2 of unit cell (ref 3a). [d] Triclinic crystal form. [e] Monoclinic crystal form.

EPR Spectroscopic Properties of Phenoxyls. The conformation that the fused heterocyclic ring adopts in a crystal of the phenol is not necessarily the same as that it adopts when the phenol is in solution. Some information regarding the solution conformation of the corresponding phenoxyl radical can be gained by EPR spectroscopy. Of greater importance is the fact that a detailed consideration of the magnitude of the hyperfine splittings (hfs) found for each phenoxyl radical provides valuable information about the extent to which the unpaired electron is delocalized in the radical. This is particularly useful because electron delocalization is expected to correlate with antioxidant activity. That is, the greater the electron delocalization the more stabilized will be the phenoxyl radical relative to the parent phenol and, hence, the weaker will be the O–H bond in the phenol and the greater will be k_1.

Most of the potentially interesting phenoxyl radicals were generated by UV photolysis of degassed solutions of the phenols in benzene/di-*tert*-butyl peroxide (5:1 (v/v)) at room temperature. Excellent spectra were generally obtained, and hyperfine splittings (hfs) were derived by comparison with computer-simulated spectra. These results are summarized in Table III.

Bimolecular Self-Reactions of Phenoxyls and the Phenoxyl–Oxygen Reaction. Under normal, in vitro, experimental conditions the phenoxyl radical produced in reaction 1 is destroyed by:

$$\mathrm{ROO\cdot} + \mathrm{ArO\cdot} \xrightarrow{\text{fast}} \text{nonradical products} \qquad (8)$$

Effective phenolic antioxidants yield phenoxyl radicals that are relatively unreactive toward one another and toward molecular oxygen.

$$\mathrm{ArO\cdot} + \mathrm{ArO\cdot} \xrightarrow{\text{slow}} \text{nonradical products} \qquad (9)$$

$$\mathrm{ArO\cdot} + \mathrm{O_2} \xrightarrow{\text{slow}} \text{radical products} \qquad (10)$$

We have measured some rate constants for reaction 9 and have examined the effect of oxygen on the decay kinetics.[1e] These results are summarized in Table IV.

Discussion

The phenols listed in Table I show quite wide variations in their reactivities toward peroxyl radicals. The k_1 values obtained by the inhibited autoxidation of styrene method are more reliable, both in a relative and absolute sense, than those obtained by the laser-flash kinetic EPR method. This is particularly true for compounds having k_1 values greater than ca. 10^6 M^{-1} s^{-1}. The

(29) This may well be the reason that $Cl_3COO\cdot$ is so much more reactive toward α-T than are alkylperoxyls (see ref 14).

(30) There are two molecules of Ib which have slightly different structures in the unit cell (see Table II).

Table III. EPR Spectral Parameters for Some Phenoxyl Radicals[a]

parent phenol	g	a^H 2	4(CH_2)	5(CH_3)	7(CH_3)	8(CH_3)	a^{other}	ΔH_{pp}[b]
α-T[c]			1.47	5.98	4.57	0.94	0.098 (2 H)[d,e]	
Ia	2.00475	3.30 (1 H)	1.41	6.02	4.64	1.00		0.25
Ia[f]		3.22 (1 H)	1.40	6.00	4.62	1.00	0.09 (2 H)[d,g]	<0.1
Ib[c]			1.46	5.94	4.51	0.96	0.101 (2 H)[d,e]	
Ib	2.00476		1.48	6.04	4.55	0.96		0.3
Id	2.00475		1.55	6.35	4.72	1.06		0.3
If	2.00477		1.60	6.15	4.60	1.00		0.4
Ig	2.00472		1.45	6.00	4.56	0.96		0.3
Ij	2.00482		1.5 (1 H), 1.7 (1 H)	6.05	4.95	1.13		0.3
IVc	2.00431	(6.5 (1 H))	(0.7)	(4.45)	(4.45)	(0.7)	(4.4 (N))	0.35
V	2.00562	5.5 (1 H)		5.60	4.50	1.35		0.35

parent phenol	g	a^H 2	3(CH_2)	4(CH_3)	6(CH_3)	7(CH_3)	ΔH_{pp}[b]
IIIa	2.00468	1.98 (1 H)	0.28	5.80	4.75	1.10	0.2
IIIb	2.00471		[h]	5.78	4.78	1.03	0.2
IIIc	2.00462		[h]	6.00	4.95	1.11	0.5

parent phenol	g	a^H OCH_3	5	6	2	3	ΔH_{pp}[b]
MeOP[i]	2.005[j]	1.75	0.85 (1 H)	5.75 (1 H)	5.75 (1 H)	0.85 (1 H)	0.5
VIa	2.00482	1.50	0.95 (1 H)	5.43 (1 H)	5.43 (1 H)	0.95 (1 H)	0.2
VIb	2.00478	2.0	1.0 (1 H)	5.5 (CH_3)	4.5 (CH_3)	1.5 (CH_3)	0.2
VIc	2.00479	<0.1	1.56 (CH_3)	6.18 (CH_3)	6.18 (CH_3)	1.56 (CH_3)	0.3

[a] In benzene/di-*tert*-butyl peroxide (5:1 (v/v)) as solvent at room temperature unless otherwise noted. For numbering, see Table I. Hyperfine splittings and line widths are given in gauss. [b] Line width. [c] Data from ref 60. [d] Position 3. [e] These hdyrogens were not resolved by EPR but were shown by ENDOR to have equal hfs of about this magnitude. [f] In toluene/di-*tert*-butyl peroxide (5:1 (v/v)) at −15 °C. [g] See Figure 3, part C. [h] Not resolved. [i] 4-Methoxyphenol. [j] Spectrum changes rapidly with time so no attempt was made to obtain a precise *g* value.

Table IV. Rate Constants for the Bimolecular Self-Reactions of Some Phenoxyl Radicals in the Absence and Presence of Oxygen[a]

parent phenol	$2k_9$ (M^{-1} s^{-1}) O_2 absent[b]	O_2 present[c]
α-T	3×10^3	3×10^3
β-T	4×10^4	5×10^4
γ-T	4.5×10^4	
δ-T	1.5×10^5	2×10^5
DMT	4.5×10^3	
Ib	3×10^3	3×10^3
IIIa	4×10^3	
IVc	6×10^4	5×10^4
V	2×10^2	7×10^2

[a] Measured by kinetic EPR in benzene/di-*tert*-butyl peroxide (10:1 (v/v)) at 23 °C at [ArOH] concentrations of 1, 5, and 50×10^{-3} M. (See ref 1e.) [b] Sample degassed and sealed under vacuum. [c] O_2 saturated at 760 torr, $[O_2]$ = ca. 9.2×10^{-3} M (see text).

Table V. Dihedral *fab* Angles, k_1 Values and Calculated O-H Bond Strengths for Some Selected Phenols.

phenol	*fab*, deg	$10^4 k_1$, M^{-1} s^{-1}	D[ArO-H],[a] kcal/mol
α-T		320	80.4
Ib	17	380	80.2
IIa	38[b]	250	80.8
IIIb	6[c]	570	79.7
VIa	8[d,e]	94	82.1
VIb	8[d,e]	130	81.6
VIc	89[e]	39	83.2

[a] Calculated from data in ref 32. See text. [b] Angle for IIb. [c] Angle for IIId. [d] Assumed to be the same as for 4-methoxyphenol. [e] See ref 3.

significance of the LKEPR data is that they confirm, in a general way, the k_1 values obtained by the inhibited autoxidation procedure. Differences in individual k_1 values obtained by the two techniques should not be considered important.

Most of the differences in k_1 values between the various phenols we have studied can be attributed to the electronic effect of the group that is para to the hydroxyl function. Effects due both to conjugative electron donation and to inductive electron withdrawal can be identified, with the former being strongly dependent on the conformation of the para group with respect to the aromatic ring. Such an orientationally dependent contribution from electron delocalization to chemical reactivity is generally referred to as a stereoelectronic effect.[31]

The influence of structural changes on k_1 values will be given detailed consideration only for α-T and those other phenols that have two methyl groups ortho to the hydroxyl function. For the other phenols two comments will suffice: (1) α-T is more reactive than β-T, γ-T, and δ-T because these three tocopherols lack one or more ortho methyl groups and such electron-releasing groups stabilize phenoxyls and therefore increase k_1 values.[6] For the same reason IIIb is more reactive than IIId. (2) The 2,6-di-*tert*-butylphenols, VIIa–c, are less reactive than the corresponding 2,6-dimethylphenols, VIa,f,g, respectively, because the presence of two ortho *tert*-butyl groups in VII hinders the approach of the peroxyl radical.

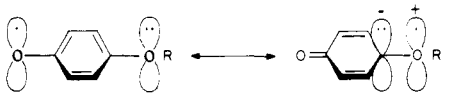
Other, more subtle, structural changes are considered below under two main headings: (1) **Stereoelectronic Effects**—which are concerned with the orientation with respect to the aromatic plane of the p-type lone pair on the heteroatom para to the hydroxyl group; and (2) **Inductive Effects**—which are concerned with the inductive effect of groups attached to position 2 of those phenols that have a fused heterocyclic ring.

Stereoelectronic Effects. (i) General Comments. Differences in the reactivities of many of the para-RX-substituted phenols listed in Table I can be quite simply accounted for in terms of extent of overlap between the p-type orbital on X and the aromatic π-electron cloud or, more specifically, in terms of the dihedral angle between the aromatic ring and the R–X bond. This angle, which is designated by *fab* in structure A (see Results and Table II), has been obtained by X-ray analysis of a crystal of a suitable phenol. To a first approximation the *fab* angle can be assumed to equal the dihedral angle, θ, between the p-type lone pair on X and the axis of the p orbital at the adjacent aromatic carbon (see A) for the phenol dissolved in an organic solvent. Stabilization of the phenoxyl radical will be maximized, and hence k_1 will be optimized, when orbital overlap is minimized, i.e., when $\theta = 0°$.

(31) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: Oxford, 1983. Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: Berlin, 1983. Easton, C. *Sci. Prog., Oxf.* **1983**, *68*, 503–517.

Stabilization will be at a minimum when these two orbitals are orthogonal, i.e., when $\theta = 90°$.

The general phenomenon can be illustrated by comparing the *fab* angles listed in Table II with the k_1 values listed in Table I. This is done for the hydroxychroman Ib, the hydroxychromene IIa, the hydroxydihydrobenzofuran IIIb, 4-methoxy-2,6-dimethylphenol VIa, 4-methoxy-2,3,6-trimethylphenol VIb, and 4-methoxytetramethylphenol VIc in Table V. For the phenols having a fused oxygen-containing heterocyclic ring but otherwise rather similar structures, viz., IIa, Ib, and IIIb, reactivity increases from 250×10^4, to 380×10^4, to 570×10^4 M^{-1} s^{-1}, respectively, as *fab* decreases from 38°, to 17°, to 6°, respectively. Similarly, although k_1 increases from 94×10^4 to 130×10^4 M^{-1} s^{-1} on going from VIa to VIb because of the radical-stabilizing effect of the additional *m*-methyl group,[6] it decreases dramatically to 39×10^4 M^{-1} s^{-1} in VIc with the addition of the second *m*-methyl group. The first two of these phenols are presumed to have *fab* angles close to 8° (the value found for 4-methoxyphenol)[3] while for the last the *fab* angle is close to 90°. Thus, for structurally related phenols there is a striking correlation between *fab* dihedral angles and k_1 values both for those compounds that have a fused heterocyclic ring and for those that do not. (Although the dihedral angles in the crystal are not necessarily the same as the dihedral angles adopted by these phenols in solution (vide infra), there is no reason to expect that the relative order in which *fab* angles increase along a series of phenols will differ dramatically from the relative order in which θ values increase.) The correlation between *fab* angle and k_1 value therefore supports our contention that, for the phenolic antioxidants with which we are dealing, stabilization of the phenoxyl radical by the p-type lone pair on the para heteroatom, i.e., C ↔ D, is influenced by the orientation of this lone pair with respect to the aromatic plane. That is, the reactivities of these phenols are subject to stereoelectronic effects.



C D

(ii) ArO–H Bond Strengths and "Activation" by a "Perpendicular" OMe Group. The stabilization energy of a phenoxyl radical, ArO·, relative to that of C_6H_5O·, is given by the difference in the O–H bond strengths, $D[C_6H_5O\text{–}H] - D$[ArO–H]. Values of D[ArO–H] can be estimated from measured values for k_1 by using a correlation (eq I) that can be derived from work reported by Mahoney and DaRooge,[32] viz.

$$D[\text{ArO–H}]\ (\text{kcal/mol}) = 100.4\ (\pm 1.1) - 3.07\ (\pm 0.20)\ \log\ (k_1/M^{-1}\ s^{-1}) \quad (I)$$

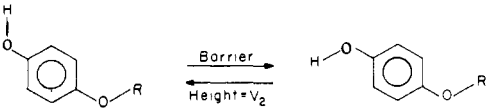
The k_1 values on which this relation is based were measured at 60 °C with peroxyl radicals derived from 9,10-dihydroanthracene.[32] Our own k_1 values have been used to derive the ArO–H bond strengths listed in Table V, no allowance having been made for the temperature difference (which would correspond to less than a factor of 2 in k_1 values) or for the type of peroxyl radical. However, it should be noted that implicit to eq I is the possibly unjustified (vide infra) assumption that the entropies of activation for reaction 1 are equal for all phenols. If we ignore this potential complication for the moment we see that, relative to 4-methoxytetramethylphenol (VIc, $\theta \sim 90°$), the phenoxyl radicals derived from IIa, α-T, Ib, and IIIb are stabilized by 2.4, 2.8, 3.0, and 3.5 kcal/mol, respectively.

It is instructive to compare these estimated O–H bond strengths with the results of Baird's[33] MNDO theoretical study of 1,4-dihydroxybenzene and the 4-hydroxphenoxyl radical. Values of $D[p\text{-}HOC_6H_4O\text{–}H]$ were calculated to be weaker than $D[C_6H_5O\text{–}H]$ by 3.8 kcal/mol when the para-O–H bond was coplanar with the ring (a value in good agreement with the 3.7 kcal/mol reported by Mahoney and DaRooge[32]) and 1.3 kcal/mol when the para O–H bond was twisted perpendicular to the ring. Our own data (Table V) imply that a change in *fab* from ca. 90° to nearly 0° decreases the ArO–H bond strength by ca. 3.5 kcal/mol rather than by the ca. 2.5 kcal/mol calculated by Baird. This difference could be due to the fact that the "effective" θ for VIc is significantly less than the measured *fab* angle. That is, H atom abstraction from VIc will become easier the further the OMe group twists from its equilibrium position perpendicular to the aromatic plane. Since there will certainly be some libration of the OMe group about the C_4–OMe bond, the "effective" value of θ may well be considerably less than 90°. This would reduce the activation energy for the reaction. However, it seems probably that this rate-accelerating effect (relative to a "fixed" $\theta = 90°$) would be more than compensated by a reduced Arrhenius preexponential factor, i.e., the rate-accelerating effect of the decreased enthalpy of activation would be outweighed by the rate-retarding effect of the increased entropy of activation. It is, of course, unlikely that there would be any significant changes in "effective" θ values for those phenols which have a fused heterocyclic ring.

Baird[33] has pointed out that the residual stabilization of 1.3 kcal/mol in the 90° twisted $p\text{-}HOC_6H_4OH$ structure is due mainly to delocalization into the ring's π-electron system in the radical from the other lone pair of the twisted OH group. That there is some stabilization of 4-methoxytetramethylphenoxyl relative to 2,3,5,6-tetramethylphenoxyl is clear from the k_1 values for VIc (3.9×10^5 M^{-1} s^{-1}) and VIg (7.5×10^4 M^{-1} s^{-1}). In fact, the "perpendicular" 4-OMe group in VIc appears to be about as activating as the 4-Me group in pentamethylphenol, VId ($k_1 = 3.6 \times 10^5$ M^{-1} s^{-1}). This result contradicts the general belief[34] that a "perpendicular" alkoxy group will be "deactivating" relative to both a methyl group and a hydrogen atom. That is, an alkoxy group is electron releasing by a resonance, or $+M$, effect (because of its p-type lone pair of electrons), but it is also electron withdrawing because of its inductive, or $-I$, effect (which arises because oxygen is more electronegative than carbon or hydrogen). If an alkoxy group is attached to an aromatic ring, is coplanar with the ring, and is "activating" relative to an alkyl group or a hydrogen atom in some physical process or chemical reaction, then it has generally been assumed that a perpendicular alkoxy would be "deactivating", i.e., the $+M$ activating effect would be inoperative in the perpendicular conformation and the influence of the alkoxy group would be manifest only by its $-I$ effect. From our results it is clear that the $-I$ effect of a perpendicular alkoxy group is more than outweighted by a residual $+M$ effect which we attribute to a resonance contribution from the other lone pair on the oxygen.

(iii) Dependence of ArO–H Bond Strengths, OH Rotational Barriers, and k_1 Values on θ. Because there is conjugative participation in the stabilization of 4-alkoxyphenoxyl radicals by two inequivalent oxygen lone pairs, the potential function for rotation is rather complicated.[33] For $\theta < 40°$ Baird's results indicate that the energy loss due to twisting is approximately proportional to $1 - \cos\theta$, and the change in $D[p\text{-}HOC_6H_4O\text{–}H]$ is $\approx 3.2(1 - \cos\theta)$ kcal/mol.[33] However, the estimated O–H bond strengths for tetraalkylated 4-alkoxyphenols of known *fab* angle (i.e., Ib, IIa, IIIb, and VIc from Table V) do not discriminate between this relation and the more conventional[1c,1d] representation of p-orbital overlap in terms of $\cos^2\theta$ (see Figure 1).

We have also found[35] that for a number of our phenols the potential barriers to rotation of the OH group, V_2 (see E ⇄ F), do not serve to discriminate between a $1 - \cos\theta$ and a $\cos^2\theta$ law (see also Figure 1). These OH rotational barriers, which were



E F

obtained by measuring low-temperature dielectric relaxation rates,

(32) Mahoney, L. R.; DaRooge, M. A. *J. Am. Chem. Soc.* **1975**, *97*, 4722–4731.

(33) Baird, N. C. *Tetrahedron* **1984**, *40*, 3383–3385.

(34) Taft, R. W. Jr.; Evans, H. D. *J. Chem. Phys.* **1957**, *27*, 1427–1428.

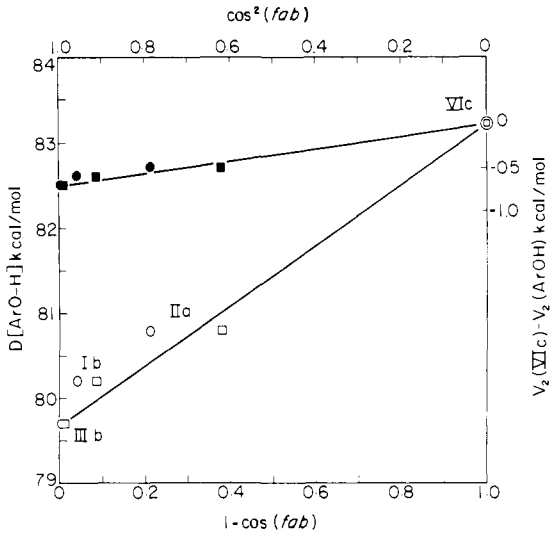


Figure 1. Open points: phenolic bond strengths, D[ArO–H], calculated from eq I plotted against 1 − cos (*fab*) (○) and against cos² (*fab*) (□). Filled points: barriers to rotation of the phenolic OH group, V_2, relative to the barrier in VIc plotted against 1 − cos (*fab*) (●) and against cos² (*fab*) (■). For the meaning of identifying symbols, see Table I.

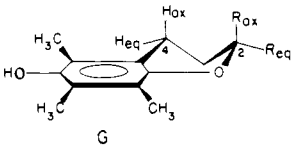
also indicate that a perpendicular alkoxy group is about as activating relative to hydrogen as is a methyl group.[35]

It is interesting to note that V_2 was found[35] to decrease by ca. 0.68 kcal/mol[36] on going from VIc ($\theta \sim 90°$, $V_2 \sim 2.4$–3.0 kcal/mol[36]) to IIIb ($\theta \sim 6°$), see Figure 1. A 4-alkoxy substituent which is coplanar with the aromatic ring therefore causes the energy difference between a conformation with a coplanar OH group (i.e., the ground state of the phenol) and a conformation with a perpendicular OH group to be 0.68 kcal/mol smaller than the energy difference between these conformations when the 4-alkoxy group is perpendicular to the ring. Abstraction of the phenolic hydrogen will occur with the OH group perpendicular to the aromatic ring in order to gain resonance stabilization by delocalization of the developing unpaired electron into the aromatic π system. Because of this difference in the energies of the ground (OH planar) and twisted (OH perpendicular) states of the two phenols, the enthalpy for H abstraction from IIIb will be 0.68 kcal/mol less than that for H abstraction from VIc. The actual difference in $\Delta G_1^{\ddagger}$ between IIIb and VIc favors H abstraction from IIIb by nearly one additional kcal/mol, i.e., $\Delta G_1^{\ddagger}$(IIIb) − $\Delta G_1^{\ddagger}$(VIc) = $-RT$ ln (573/39) = 1.6 kcal/mol. In summary, therefore, a phenol with a coplanar *p*-alkoxy group has enhanced antioxidant activity relative to a phenol with a perpendicular alkoxy group for two reasons. First, the coplanar alkoxy group reduces the energy, V_2, required to twist the OH group from its preferred coplanar position (see E ⇄ F) to a perpendicular position by ~0.7 kcal/mol. Second, the coplanar alkoxy group stabilizes the transition state for reaction by increasing the delocalization of the unpaired electron in the developing phenoxyl radical (see C ↔ D), producing an additional diminution of $\Delta G_1^{\ddagger}$ of ~0.9 kcal/mol.

(iv) The Hypothetical "Planar" 4-Methoxytetramethylphenol. Would such a species be as good an antioxidant as a phenol such as IIIb in which (virtual) coplanarity is enforced by the heterocyclic ring? In an attempt to answer this question, we examine first the enhancement in k_1 produced by an additional, but nonhindering, *m*-methyl group. The ratio of k_1 values for the following phenol pairs are as follows: α-T/DMT, 1.79; VIb/VIa, 1.38; VId/VIe, 3.27; VIe/VIf, 1.29; and $^1/_2$VIg/VIh = $^1/_2$3 = 1.5. Since 4-methoxy-2,3,6-trimethylphenol, VIb, has a k_1 value of 1.3 × 10⁶ M^{-1} s^{-1} and IIIb has a k_1 value of 5.7 × 10⁶ M^{-1} s^{-1}, the enhancement in k_1 produced by ring closure and the consequent addition of a *m*-alkyl group amounts to a factor of 5.7/1.3 = 4.4. This is considerably larger than any of the above-listed *m*-methyl group-enhancement factors. We therefore conclude that the heterocyclic ring provides a more efficient antioxidant than would a hypothetical "planar" 4-alkoxytetramethylphenol. We presume that the origin of this heterocyclic ring effect lies in entropic factors.[37] That is, it is necessary to "freeze-out" the libration of the 4-OMe group about the C_4–O bond in the transition state for H abstraction from VIb but not from IIIb. This means that the bond strengths calculated from eq I for phenols having a fused heterocyclic ring (Table V and Figure 1) are probably smaller than their true values. The difference in D[ArO–H] between VIc and IIIb will therefore be less than the calculated 3.5 kcal/mol and so would be in better agreement with Baird's[33] calculations (vide supra).

It should perhaps be emphasized that the foregoing discussions assume that the mechanism of reaction 1 remains the same for all the phenols examined in this work. That this is the case is implied by the fact that phenols having quite widely different k_1 values all exhibit substantial deuterium kinetic isotope effects (see Results).

(v) "Puckering" of the Heterocyclic Ring and Effect of Different Heteroatoms. The heterocyclic ring in the hydroxychromans has a half-chair conformation in the crystal with the extent of ring puckering being to some extent limited by a 1,3 steric interaction between the pseudoaxial hydrogen at the 4-position, H_{ax}, and the pseudoaxial substituent at the 2 position, R_{ax}, see G. Replacing



G

both 2-CH_3 groups in Ib by hydrogen to form Ia will permit ring puckering to increase. As a consequence, θ will increase and so k_1 will decrease, as is observed (see Table I). Similarly, in the replacement of one of the 2-CH_3 groups in Ib by the bulky phytyl group to form α-T the remaining methyl group (which is expected to reside in the axial position) will probably be pushed closer to H_{ax}. That is, θ is expected to be larger in α-T than in Ib and k_1 to be smaller, as is observed. (The lower reactivities of Ic–j relative to **Ib** we attributed *mainly* to polar factors, vide infra).

Some puckering of the heterocyclic ring in IIIa induced by a 1,2 steric interaction between the CH_3 group in position 2 and the eclipsed H in position 3 may be the reason that IIIa is somewhat less reactive than IIIb.

An unfavorable conformation of the heterocyclic ring in IVc also provides a simple explanation for the relatively low reactivity of this compound. That is, we had expected that IVc would be a better antioxidant than Ia because nitrogen, being less electronegative than oxygen, would be better able to stabilize a neighboring radical center by conjugative delocalization of its lone pair of electrons.[38] However, an inspection of space-filling models indicated that there would be very severe steric interactions between an equatorial *N*-ethyl group and the methyl group at position 8 on the aromatic ring. As a consequence, we presume[39] that the *N*-ethyl group adopts the axial position, as in H, with the nitrogen lone pair lying rather close to the plane of the aromatic ring, i.e., in a relatively unfavorable position to stabilize the incipient phenoxyl radical.

It is obvious that the steric interaction present in IVc (and IVb)[40] would be much less with the ethyl group replaced by a

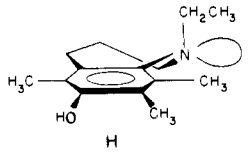
(35) Gilchrist, J. le G.; Burton, G. W.; Ingold, K. U. *Chem. Phys.* **1985**, *95*, 473–481.

(36) Differences in V_2 between phenols have been determined with much more precision than the absolute value of V_2 for any of the phenols mentioned.[35]

(37) We tend to rule out a Mills-Nixon effect as the origin of the enhanced activity of the phenols having a fused heterocyclic ring, see: Mitchell, R. H.; Slowey, P. D.; Kamada, T.; Williams, R. W.; Garratt, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 2431–2432. For a contrary view, see: Hiberty, P. C.; Ohanessian, G.; Delbecq, F. *J. Am. Chem. Soc.* **1985**, *107*, 3095–3100.

(38) See e.g.: Burkey, T. J.; Castelhano, A. L.; Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1983**, *105*, 4701–4703.

(39) Crystals suitable for X-ray analysis could not be obtained.



H

hydrogen atom, i.e., IVa. However, this compound was found to be unstable in air even in the crystalline state. It was not, therefore, used as an antioxidant though it must be fairly reactive toward peroxyl radicals since they should be able to abstract hydrogen from either heteroatom.[41] The low reactivity of IVb can be attributed to polar factors (vide infra).

The formation of V by reaction of 4-mercapto-2,3,6-trimethylphenol with 3-methyl-2-buten-1-ol following the general procedure used to prepare Ib from trimethylhydroquinone was somewhat unexpected because similar routes have been used to prepare purported sulfur analogues of α-T.[42,43] There can be no doubt regarding the structure of V, since it was confirmed by X-ray analysis. We consider it probable that if hydroxydihydrothiobenzopyrans have been made by others[42,43] they will also have the two alkyl groups that are attached to the heterocyclic ring, joined to the 4-position and not to the 2-position as claimed. It is probably inappropriate to compare the reactivity of V with that of any other compound listed in Table I both because of its different structure and because the stoichiometric factor for V was only ca. 1.5 rather than ca. 2.0 as found for all other compounds in this table.[44] Nevertheless, it is worth noting that sulfur is generally considered to be more effective than oxygen at stabilizing a neighboring radical center[46] and that the relatively small *fab* angle in V (see Table II) is consistent with a relatively large value for k_1.[47]

Inductive Effects. A number of food preservation tests have shown that Ic is superior to α-T as an antioxidant.[49-52] Since Ic is less reactive toward peroxyl radicals than α-T in homogeneous nonpolar solvents (see Table I), its effectiveness in food preservation must have some other origin. Similarly, Id and Ie were less effective food preservatives than Ic,[49] although both compounds are more reactive toward peroxyl radicals.

The decreased reactivity of Ic–f and Ii and Ij, relative to Ib, we attribute *principally* to the electron-withdrawing nature of the various R_2 groups. The inductive,[53,54] or field,[55] effect of these electron-withdrawing groups will impair the ability of the 2p-type lone pair on the ring oxygen to participate in the stabilization of the phenoxyl radical. That is, an electron-withdrawing substituent in the neighborhood of the heteroatom could reduce k_1 even if the dihedral angle, θ, between the axis of the 2p-type lone pair and the axis of the p orbital at the adjacent aromatic carbon remains the same (as appears to be roughly the case for Ib and Ic, see *fab* angles given in Table II). In solution the value of θ may vary somewhat with substituent. For this reason, the correlation shown in Figure 2 between the log $(k_1/M^{-1}\ s^{-1})$ values for all the phenols from class I that have $R_1 = CH_3$ and the σ_I substituent constants[54] of their respective R_2 group is considerably better than might reasonably have been expected. The line drawn in this figure (which ignores the point for Ic) has a slope $\rho = -1.25$. It would appear that when a carboxylic acid group is close to the oxygen atom in the heterocyclic ring that it may have a specific deactivating effect, possibly associated with hydrogen bonding, since the σ_I value for C(O)OH (0.30) is actually less than that for C(O)OMe (0.32)[54,56] (cf. also Ie vs. If).

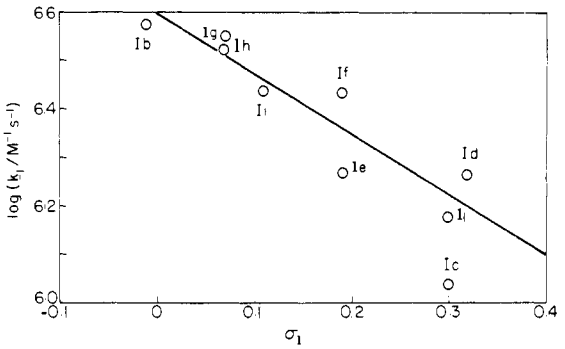


Figure 2. Plot of log $(k_1/M^{-1}\ s^{-1})$ for phenols from class I having $R_1 = CH_3$ vs. the σ_I values for their respective R_2 substituents. The σ_I values are from ref 54. Since σ_I values were not available for the R_2 substituents of Ie and Ig, these values have been assumed to be the same as those for the corresponding ester groups (If and Ih, respectively). For the meaning of identifying symbols, see Table I.

The differences in reactivity between IIa and IIb and between IIIb and IIIc can also be attributed to the inductive effect of the carboxylate group. The magnitude of this effect decreases, and hence k_1 increases, the further the carboxylate group is from C_2, cf. Ic vs. Ie vs. Ig, and Id vs. If vs. Ih. The very low reactivity of the amide IVb compared with the amine IVc can also be attributed to the polar effect of the acetyl group ($\sigma_I = 0.30$).[54] In this case, the electron-withdrawing substituent is directly attached to the heteroatom and so the effect is particularly dramatic.

Inductive effects may also explain the exceptional food-preserving properties of Ic.[58] This is because the CO_2H group will be ionized at the pH of most food products that contain moisture and the CO_2^- group is, inductively, quite strongly electron releasing ($\sigma_I = -0.19$,[54] $F = -0.27$[55a]).

(40) Svensson, K. G.; Nilsson, J. L. G. *Acta Pharm. Suec.* **1973**, *10*, 277–284.

(41) 6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (ethoxyquin) and related compounds are known to be excellent antioxidants at temperatures below 100 °C. See e.g.: Nekipelova, T. D.; Gagarina, A. B. *Dokl. Akad. Nauk SSSR* **1976**, *226*, 626–629. Nekipelova, T. D.; Gagarina, A. B.; Emanuel, N. M. *Ibid.* **1978**, *238*, 392–395. Lobanova, T. V.; Kasaikina, O. T.; Ivanov, Yu. A.; Shapiro, A. B.; Gagarina, A. B. *Ibid.* **1979**, *245*, 643–646. Kasaikina, O. T.; Kartasheva, Z. S.; Lobanova, T. V.; Rusina, I. F.; Ivanov, Yu. A.; Gagarina, A. B. *Neftkhimiya* **1982**, *22*, 265–271. Kasaikina, O. T.; Lobanova, T. V.; Fentsov, D. V.; Ivanov, Yu. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1983**, 2214–2218. Kasaikina, O. T.; Lobanova, T. V.; Fentsov, D. V. *Ibid.* **1983**, 2219–2223.

(42) Karrer, P.; Leiser, P. *Helv. Chim. Acta* **1944**, *27*, 678–684.

(43) Valashek, I. E.; Shakhova, M. K.; Samokhvalov, G. I. *Zh. Org. Chim.* **1982**, *18*, 2497–2500.

(44) Unusual stoichiometric factors have been reported for other sulfur-containing chain-breaking antioxidants.[45]

(45) Gardner, D. V.; Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1964**, *42*, 2847–2851.

(46) See e.g.: Biddles, I.; Hudson, A.; Whiffen, J. T. *Tetrahedron* **1972**, *28*, 867–874. Wayner, D. D. M.; Arnold, D. R. *Can. J. Chem.* **1984**, *62*, 1164–1168. Nonhebel, D. C.; Walton, J. C. *J. Chem. Soc., Chem. Commun.* **1984**, 731–732. Griller, D.; Nonhebel, D. C.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1817–1821. Luedtke, A. E.; Timberlake, J. W. *J. Org. Chem.* **1985**, *50*, 268–270.

(47) The value of k_1 was obtained by means of an equation that avoids the requirements to know the stoichiometric factor.[3b,48]

(48) Tsepalov, V. F.; Kharitonova, A. A.; Gladyshev, G. P.; Emanuel, N. M. *Kinet. Katal.* **1977**, *18*, 1261–1267. Kharitonova, A. A.; Kozlova, Z. G.; Tsepalov, V. F.; Gladyshev, G. P. *Ibid.* **1979**, *20*, 593–599.

(49) Scott, J. W.; Cort, W. M.; Harley, H.; Parrish, D. R.; Saucy, G. *J. Am. Oil Chem. Soc.* **1974**, *51*, 200–203.

(50) Cort, W. M.; Scott, J. W.; Arauj, M.; Mergens, W. J.; Cannalonga, M. A.; Osadca, M.; Harley, H.; Parrish, D. R.; Pool. W. R. *J. Am. Oil Chem. Soc.* **1975**, *52*, 174–178.

(51) Cort, W. M.; Scott, J. W.; Harley, J. H. *Food Tech. (Chicago)* **1975**, *29*, 46–50.

(52) Scott, J. W.; Cort, W. M. *Cosmet. Toiletries* **1976**, *91*, 39–44.

(53) Exner, O. In "Advances in Linear Free Energy Relationships"; Chapman, N. B., Shorter, J. S., Eds.; Plenum Press: New York, 1972; Chapter 1.

(54) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119–251.

(55) (a) Swain, C. G.; Unger, S. H.; Rosenquist, N. R.; Swain, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 492–502. (b) For some critical comments on this paper see: Reynolds, W. F.; Topsom, R. D. *J. Org. Chem.* **1984**, *49*, 1989–1992. Hoefnagel, A. J.; Oosterbeek, W.; Wepster, B. M. *Ibid.* **1984**, *49*, 1993–1997. Charton, M. *Ibid.* **1984**, *49*, 1997–2001. Swain, C. G. *Ibid.* **1984**, *49*, 2005–2010. Marriott, S.; Reynolds, W. F., Topsom, R. D. *Ibid.* **1985**, *50*, 741–743.

(56) Swain's[55a] F values show a similar difference, viz., F(C(O)OH) = 0.44, F(C(O)OR) = 0.47, but Inamoto's[57] ι values are identical for these two substituents.

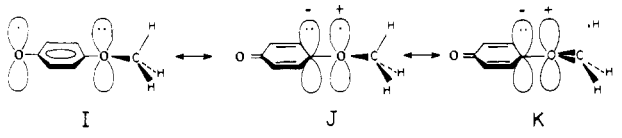
(57) Inamoto, N.; Masuda, S. *Chem. Lett.* **1982**, 1007–1010.

(58) Of course, other properties unique to Ic may also be involved in food preservation such as its greater mobility between aqueous and lipid regions in the food compared to α-T,[59] or its presumed ability to chelate catalytic metal ions.

(59) Doba, T.; Burton, G. W.; Ingold, K. U. *Biochem. Biophys. Acta* **1985**, *835*, 298–303. Niki, E.; Kawakami, A.; Saito, M.; Yamamoto, Y.; Tsuchiya, J.; Kamiya, Y. *J. Biol. Chem.* **1985**, *260*, 2191–2196.

EPR Spectroscopic Evidence Regarding the Structure and Stabilization of Phenoxyl Radicals. The hfs assignments for the chromanoxyls that are given in Table III are based on those of Mukai et al.[60] for the radicals derived from α-T and Ib which are also given in this table. The hfs for the phenoxyls derived from the dihydrobenzofurans IIIa–c, the dihydrobenzothiopyran V, and 4-methoxytrimethylphenol VIb were assigned by analogy. Hfs assignments for the phenoxyls from 4-methoxyphenol and its 2,6-dimethyl (VIa) and tetramethyl (VIc) substituted derivatives are obvious. Although a reasonably good fit between measured and simulated spectra was obtained for the radical derived from the tetrahydroquinoline IVc by using the listed hfs, these numbers have been placed in parentheses because the fit is unlikely to be unique. That is, it is highly improbable that the H hfs for the 5- and 7-CH_3 groups, the N atom, and the CH_2 of the ethyl group should all be accidentally equivalent. A proper assignment of hfs for this radical would have required a number of specifically deuterated compounds. However, the benefit that would have been gained from this information did not, in our view, justify such a massive synthetic effort. Finally, under these conditions spectra too weak to allow firm hfs assignments to be made were obtained from Ic and the chromenoxyl derived from IIa.

An interesting conformational effect can be observed in the EPR spectra of the phenoxyl radicals derived from 4-methoxyphenol and its methylated derivatives, VIa–c.[61] For those radicals which have at least one non-methylated meta position, hfs by the methoxyl group's hydrogens are readily observed ($a^H(OCH_3)$ = 1.5–2.0 G). Spin reaches these H atoms by hyperconjucation via the 2p-type lone pair on the methoxyl oxygen, I ↔ J ↔ K. In



I J K

VIc steric interactions between the two *m*-methyl groups and the methoxy group force the latter into a position perpendicular to the aromatic ring (*fab* = 88.6°). For this reason, little or no spin reaches the 2p lone pair and so none can reach the H atoms of this methoxyl group ($a^H(OCH_3)$ < 0.1 G). One natural, but interesting, consequence is that the spin must remain on the phenoxyl oxygen *and* on the aromatic ring. There is, therefore, more spin density on the aromatic ring, and this spin density concentrates itself on the aromatic carbon atoms at the ortho positions (where it is "visible") and at the para position (where it is "invisible"). Spin density at the ortho aromatic carbon atoms is directly monitored by the hfs of the H atoms of the *o*-methyl groups. The "visible" increase in spin density at this position in VIc manifests itself, therefore, as a significant increase in $a^H(o\text{-}CH_3)$ in the phenoxyl derived from this radical (6.18 G) compared with the values in the radicals from VIa (5.43 G) and VIb (4.50 and 5.50 G).

It is interesting to note that the orientation of the methoxyl group with respect to the aromatic plane has no effect on the *g* values of this series of phenoxyls. This would certainly not be the case for 4-XCH_3-substituted phenoxyls in which X came from the second (e.g., sulfur[62,63]) or third row (e.g., selenium[64,65]) of the periodic table and so had a higher spin–orbit coupling constant than oxygen. In fact, the only phenoxyl *g* values to differ significantly from the 2.0046–2.0048 found for radicals having an oxygen atom para to the phenoxyl oxygen are those for the radicals with a nitrogen atom (IVc, 2.0043) and with a sulfur atom (V, 2.0056) in this position.[66]

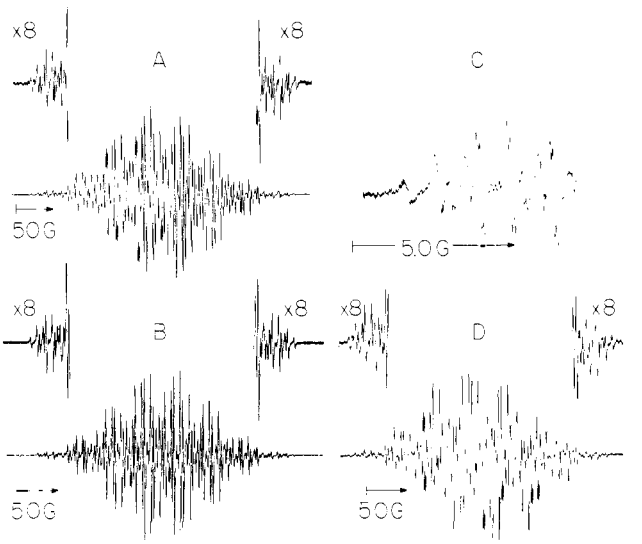


Figure 3. EPR spectrum of phenoxyl radical formed from Ia in toluene/di-*tert*-butyl peroxide (5:1 (v/v)): (A) measured at −15 °C and a modulation amplitude of 0.1 G; (B) computer simulation of A with use of the hyperfine splitting values given in Table III; (C) amplified and expanded low-field wing of the spectrum recorded at −15 °C and a modulation amplitude of 0.02 G; (D) measured at room temperature and a modulation amplitude of 0.1 G. The total spectral width in D is 0.25 G larger than in A and some distortion of the signal is apparent. The high- and low-field wings of the A, B, and D spectra are also shown at 8 times the gain of the central spectrum.

The chromanoxyl radicals, including α-tocopheroxyl, have interesting EPR spectra.[1d,60,67] The two H atoms on C-4 are magnetically equivalent for all but one of these radicals. The exceptional radical is that formed from Ij. This radical is unique in having a heteroatom directly bonded to C-2. In terms of structure G, it seems likely that Ij has R_{ax} = OCH_3 and R_{eq} = CH_3 since this will miminize the 1,3 steric interaction between the groups attached to C-2 and the pseudoaxial hydrogen on C-4. The magnetic inequivalence of H_{ax} and H_{eq} may be due to a greatly enhanced puckering of the heterocyclic ring (relative to Ib) which could explain why Ij is less reactive than Id (see Figure 2). Alternatively, there may be some specific interaction between H_{ax} and the oxygen atom of the methoxyl group.

The fact that the two H atoms on C-4 are magnetically equivalent has previously been specifically pointed out by Mukai et al.[60] for α-T and Ib. In addition, these workers showed by ENDOR that the two H atoms on C-3 (which they could not resolve by EPR, though we have achieved a partial resolution for the radical from Ia, vide infra) are also equivalent.[60] On this basis, they suggested that the heterocyclic ring was coplanar with the aromatic ring. This is, of course, inconsistent with our X-ray structures for Ib and Ic which show that the dihedral angles, *def*,

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

(61) Our values for the EPR spectral parameters for the phenoxyls derived from 4-methoxyphenyl, VIa, and VIc are in satisfactory agreement with those reported by other workers, see: Uber, W.; Stegman, H. B. In "Landolt-Börnstein, New Series, Magnetic Properties of Free Radicals"; Fischer, H., Hellwege, K.-H., Eds.; Springer-Verlag: Berlin, 1979; Vol. 9, Chapter 8, Part c2, pp 29–214.

(62) Gilbert, B. C.; Larkin, J. P.; Norman, R. O. C. *J. Chem. Soc., Perkin Trans. 2* **1973**, 272–277.

(63) Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 4727–4732.

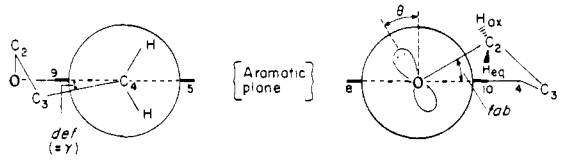
(64) Scaiano, J. C.; Ingold, K. U. *J. Phys. Chem.* **1976**, *80*, 1901–1908.

(65) Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1977**, *99*, 2079–2084.

(66) Nitrogen and sulfur have respectively smaller and larger spin–orbit coupling constants than oxygen, see: Morton, J. R.; Rowlands, J. R.; Wiffen, D. H. National Physical Laboratory (U.K.), Publ. BPR 13, 1962.

(67) For other EPR spectroscopic studies of α-tocopheroxyl and related radicals which postdate the corrected hfs assignments given in ref 60, see: Mukai, K.; Tsuzuki, N.; Ouchi, S.; Fukuzawa, K. *Chem. Phys. Lipids* **1982**, *30*, 337–345. Matsuo, M.; Matsumoto, S. *Lipids* **1983**, *18*, 81–86. Mukai, K.; Morimoto, C.; Ishizu, K. *Tetrahedron Lett.* **1983**, *24*, 5099–5102. Matsuo, M.; Matsumoto, S.; Ozawa, T. *Org. Mag. Reson.* **1983**, *21*, 261–264. Tsuchiya, J.; Niki, E.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 229–232. Bascetta, E.; Gunstone, F. G.; Walton, J. C. *Chem. Phys. Lipids* **1983**, *33*, 207–210. Mukai, K.; Takamatsu, K.; Ishizu, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3507–3510. Eloranta, J.; Hämäläinen, E.; Salo, E.; Mäkelä, R.; Kekäläinen, U. *Acta Chem. Scand. A* **1983**, *A37*, 383–391. Note that in the last mentioned reference (which deals in part with solvent effects on the hfs of α-tocopheroxyl) the assignments of hfs to the 5 CH_3 and 7 CH_3 groups are incorrect.

between the C_3–C_4 bond and the aromatic ring are ca. 11° and ca. 17°, respectively (see Table II and structure L). That is, in magnitude the *def* angles are comparable to the *fab* angles (i.e., γ is comparable to θ; see **L** and M). The EPR data for the chromanoxyl radicals and the X-ray data for the chroman molecule would, of course, be consistent if, in solution, the half-chair to half-chair interconversion of the heterocyclic ring was rapid (on the EPR time scale). This seems possible for the radical derived from Ib and for related 2,2-disubstituted 5,7,8-trimethylchromanoxyls since Mukai et al.[68] have recently reported that in an ENDOR study of the 7-*tert*-butyl-2,2,5-trimethylchromanoxyl radical the methylene hydrogens at C-4 and also those at C-3 become magnetically inequivalent at temperatures below −80 °C. This result implies that the heterocyclic ring has a nonplanar equilibrium geometry but that ringflip is rapid at room temperature.



L M

In view of the foregoing, it is surprising to find that at, and below, room temperature the radical from Ia shows hfs by only one of the pair of hydrogens at C-2 (see Table III and Figure 3).[69] Despite this, all other hfs for the Ia derived radical are very similar to those of the Ib derived radical (see Table III), and at −15 °C we even managed to achieve a partial resolution of the pair of hydrogens at C-3 (see Figure 3). At room temperature the EPR spectrum shows some changes (see Figure 3), and these may be associated with some slight motion of the heterocyclic ring. However, the change in the spectrum is not large and there is no sign that the two hydrogens at C-2 are becoming equivalent. The heterocyclic ring of the Ia derived radical must therefore be conformationally locked on the EPR time scale with a pseudoaxial H-2 ($a^H(H_{ax})$ = 3.30 G) and a pseudo-equatorial H-2 ($a^H(H_{eq})$ < 0.25 G).[70] Since the two hydrogens in position 4 of the radical derived from Ia are magnetically equivalent, we conclude that *in solution* this radical adopts a conformation somewhere between the half-chair seen in the crystal structure of Ib and Ic and a type of envelope in which the *def* angle is somewhat reduced with respect to its value in the crystal while the *fab* angle (and hence θ) may be somewhat increased. From the general similarity of the H hfs in our chromanoxyl radicals (Table III) we assume that α-tocopheroxyl and all structurally related radicals adopt generally similar conformations. We tentatively suggest two possible explanations of the difference between our EPR result for the Ia derived radical and Mukai et al.'s[68] ENDOR result on their 2,2-dimethyl-substituted chromanoxyl. One possibility is that there is a localized torsion in the heterocyclic ring by which C-3 oscillates between the position shown in structure L and a position above the aromatic plane, while C-2 remains above this plane. Such a motion would allow the two hydrogens on C-4 to become magnetically equivalent while those at C-2 remained inequivalent. An alternative possibility is that there is somewhat greater ring puckering in Ia than in Mukai et al.'s radical. This would arise because of the smaller steric interaction between 4-H_{ax} and 2-R_{ax} when R = H compared with R = CH_3, vide supra and structure G.

The reduced reactivity toward peroxyl radicals of α-T, Ia, Ic–f, and Ii and Ij relative to Ib is due to impaired ability of the 2p-type lone pair on the ring oxygen to participate in the delocalization of the unpaired electron and hence in stabilization of the phenoxyl radical. As discussed above, this impairment may be due to conformational effects in the heterocyclic ring (probably the situation insofar as α-T and Ia (and also, possibly Ij, vide supra) are concerned) or to polar factors (probably the principal cause of the reduced activity Ic–f and Ii–Ij, though H bonding may also play a role in Ic and Ie). Whatever the origin of the reduced stabilization of the phenoxyl there should be an increase in the spin density in the aromatic ring and this should be reflected in the hfs of the 5-CH_3 and 7-CH_3 groups. For the radicals derived from class I phenols there is, in fact, a rough correlation between log (k_1/M^{-1} s^{-1}) and $\sum a^H$(5-CH_3 + 7-CH_3), see Figure 4. A similar correlation between log (k_1/M^{-1} s^{-1}) and $\sum a^H$(2-CH_3 + 6-CH_3) exists for the 4-methoxy-2,6-dimethylphenoxyl radicals (see also Figure 4). Thus, within the classes considered in the present work the better antioxidants yield more stabilized phenoxyl radicals and these, naturally, have lower spin densities in their aromatic rings.

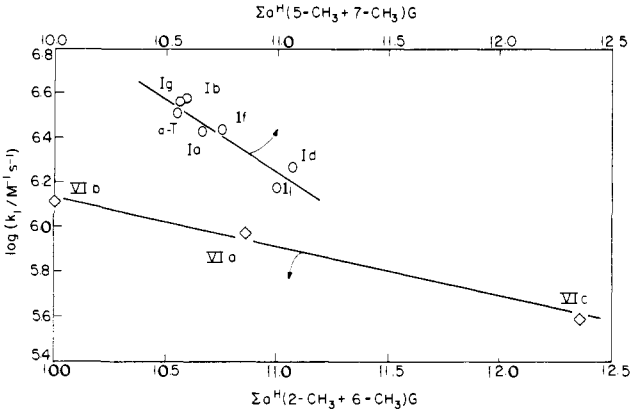


Figure 4. Plot of log (k_1/M^{-1} s^{-1}) (from Table I) vs. the sum of the hydrogen hfs by the two *o*-methyl groups in the corresponding radical (from Table III). Phenols of class I (○). Phenols of class VI (◇). For the meaning of identifying symbols, see Table I.

Decay of Phenoxyl Radicals. Lack of Effect of Oxygen. α-Tocopherol and related phenols are highly effective antioxidants because they react exceptionally rapidly with peroxyl radicals *and* because the ArO· "wasting" reactions 9, 10, 11, and 12 are relatively slow.[71]

$$\text{ArO}\cdot + \text{RH} \xrightarrow{\text{slow}} \text{ArOH} + \text{R}\cdot \qquad (11)$$

$$\text{ArO}\cdot + \text{ROOH} \xrightarrow{\text{slow}} \text{ArOH} + \text{ROO}\cdot \qquad (12)$$

The bimolecular self-reaction of α-tocopheroxyl is very slow for a radical–radical reaction, but it should be noted that our value of $2k_9$ for this radical (Table IV) is considerably larger than previously reported values.[72-74] This is due to the fact that the kinetics of decay of many ArO· radicals are complicated by the reversible formation of diamagnetic dimer and/or disproportionation products.[1e,75-78] Our own experiments were carried out

(68) Mukai, K.; Tsuzuki, N.; Ishizu, K.; Ouchi, S.; Fukuzawa, K. *Chem. Phys. Lipids* **1984**, *35*, 199–208.

(69) Note that V and probably IVc also show hfs by only one H at the 2-position.

(70) The magnitude of $a^H(H_{ax})$ and $a^H(H_{eq})$ for the H atoms attached to C-2 will depend on the spin density at the 1-oxygen atom and on the dihedral angle between this oxygen's 2p-type lone pair and the C_2–H bond in question. With certain assumptions, we estimate that the maximum probable value for $a^{H_{ax}}$ would be ca. 4 G.

(71) Although reaction 11 can occur with α-tocopheroxyl (see: Peers, K. E.; Coxon, D. T.; Chan, H. W.-S. *J. Sci. Food Agric.* **1981**, *32*, 898–904. Peers, K. E.; Coxon, D. T. *Chem. Phys. Lipids* **1983**, *32*, 49–56. Coxon, D. T.; Peers, K. E.; Rigby, N. M. *J. Chem. Soc., Chem. Commun.* **1984**, 67–68) there is no evidence that it is fast; reaction 12 must also be slow because with α-tocopheroxyl it will be endothermic by ca. 8 kcal/mol.

(72) Repges and Sernetz (Repges, R.; Sernetz, M. *Ber. Bunsenges. Phys. Chem.* **1969**, *73*, 264–267) give 180 M^{-1} s^{-1} in $CHCl_3$.

(73) Simic (Simic, M. G. In "Autoxidation in Food and Biological Systems"; Simic, M. G.; Karel, M., Eds.; Plenum Press: New York, 1980; pp 17–26) gives 350 M^{-1} s^{-1} in cyclohexane.

(74) Tsuchiya et al. (Tsuchiya, J.; Niki, E.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 229–232) give 0.061 M^{-1} s^{-1} in benzene.

(75) Weiner, S. A. *J. Am. Chem. Soc.* **1972**, *94*, 581–584.

(76) Mahoney, L. R.; Weiner, S. A. *J. Am. Chem. Soc.* **1972**, *94*, 585–590.

(77) Weiner, S. A.; Mahoney, L. R. *J. Am. Chem. Soc.* **1972**, *94*, 5029–5033.

with "fresh" α-tocopheroxyl, and decay followed clean second-order kinetics for 80% or more of the reaction.

With the exception of the radical derived from V, the rate constants for phenoxyl radical decay in oxygen-saturated (760 torr) solutions were not significantly different from the values obtained under oxygen-free conditions (see Table IV), which indicates that $k_{10} \ll 2k_9[\mathrm{ArO}\cdot]/[\mathrm{O_2}]$. Under these conditions the oxygen concentration is ca. 9.2×10^{-3} M.[28] In a typical experiment the initial α-tocopheroxyl radical concentration was ca. 2×10^{-5} M and, hence, k_{10} must be $\ll 6.5$ M^{-1} s^{-1} for this radical. The $C_6H_5O\cdot$ radical has also been shown to be unreactive toward oxygen on the time scale of its bimolecular self-reaction,[28] which is, however, diffusion controlled.[79] The 2,4,6-tri-*tert*-butylphenoxyl/O_2 reaction appears to be the only other phenoxyl/oxygen reaction to have been investigated kinetically.[80] Decay follows termolecular kinetics,[80] and k_{13} can be calculated to be ca. 3×10^5 M^{-2} s^{-1} at 25 °C. If α-tocopheroxyl reacts with oxygen in a similar manner then $k_{13} \ll 2k_9[\mathrm{ArO}\cdot]^2/[\mathrm{ArO}\cdot]^2[\mathrm{O_2}] = 3 \times$

$$2\mathrm{ArO}\cdot + \mathrm{O_2} \rightarrow \text{nonradical products} \qquad (13)$$

10^5 M^{-2} s^{-1}. That is, α-tocopheroxyl is even less reactive toward oxygen than is tri-*tert*-butylphenoxyl. We conclude that the slowness of the reaction between α-tocopheroxyl and oxygen is yet one more reason why α-T appears to have been selected as nature's major lipid-soluble, chain-breading antioxidant.[1b]

Experimental Section

Materials. Commericial samples of **(*R*,*R*,*R*)-α-tocopherol** (α-T; Eastman), **(*R*,*R*,*R*)-γ-tocopherol** (γ-T; Eastman), ***rac*-5,7-dimethyltocol** (DMT; Supelco), **2,3,4,6-tetramethylphenol** (VIe; Aldrich), **2,6-dimethylphenol** (VIh; Aldrich), **2,6-di-*tert*-butyl-4-methylphenol** (VIIb; Aldrich), and **2,6-di-*tert*-butylphenol** (VIIc, Eastman) were used without further purification. **2,4,6-Trimethylphenol** (VIf) was a sample of recrystallized material used in previous studies.

(*R*,*R*,*R*)-β-Tocopherol (β-T), **(*R*,*R*,*R*)-δ-tocopherol** (δ-T), **6-hydroxy-2,2,5,7,8-pentamethylchroman** (Ib), **2,3,5,6-tetramethyl-4-methoxyphenol** (VIc), **pentamethylphenol** (VId), **2,3,5,6-tetramethylphenol** (VIg), and **2,6-di-*tert*-butyl-4-methoxyphenol** (VIIa) were obtained as described previously.[3b] **6-Hydroxy-5,7,8-trimethylchroman** (Ia), **2,3-dihydro-5-hydroxy-2,4,6,7-tetramethylbenzofuran** (IIIa), and **2,3-dihydro-5-hydroxy-2,2,6,7-tetramethylbenzofuran** (IIId) were gifts from Drs. F. M. Dean and L. H. Sutcliffe (University of Liverpool, Liverpool, England). Ia and IIId were used as received. ^{1}H NMR and thin-layer chromatography of a sample of IIIa revealed the presence of a small amount of an impurity. Gas chromatography–mass spectrometry of the trimethylsilyl ethers indicated that the impurity represented about 5% of the mixture and was 2 mass units less than IIIa. The sample was purified by "flash" chromatography on silica gel[81] with 8% ethyl acetate in hexane (v/v). The impurity was tested by the inhibited-autoxidation method and was found to possess only weak antioxidant properties. **6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid** (Ic), **methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate** (Id), **6-hydroxy-2,5,7,8-tetramethylchroman-2-acetic acid** (Ie), **6-hydroxy-2,5,7,8-tetramethylchroman-2-propionic acid** (Ig), **6-hydroxy-2-(hydroxymethyl)-2,5,7,8-tetramethylchroman** (Ii), **6-hydroxy-2,5,7,8-tetramethyl-2*H*-chromen-2-acetic acid** (IIb), and **2,3-dihydro-5-hydroxy-2,4,6,7-tetramethylbenzofuran-2-carboxylic acid** (IIIc) were gifts from Dr. J. W. Scott (Hoffman-LaRoche, Nutley, NJ) and were used as received.

Unless otherwise noted, in the synthetic procedures described below reactions were carried out under an atmosphere of argon and solvents were dried by refluxing over CaH_2 followed by fractional distillation under argon. Column chromatography was performed by the "flash" method[81] with Merck silica gel grade 60, 230–400 mesh. The progress of a reaction was usually monitored by thin-layer chromatography (TLC) with BDH (Merck) silica gel 60 F-254 plates. These plates were generally developed with use of a 12% ethyl acetate:*n*-hexane (v/v) solution and spots were visualized with use of a phosphomolybdic acid spray (3.5%, Merck) followed by heating. Melting points were determined on a Fisher Digital Melting Point Apparatus and are uncorrected. ^{1}H NMR spectra were generally measured on a Varian EM-360A spectrometer, and chemical shifts are reported relative to Me_4Si as an internal standard. Mass spectra were measured on a Hewlett Packard 5995 GC/MS with a 10 m × 0.2 mm i.d., Ultra 1 (OV-101) column.

The methyl esters, **methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-acetate** (If) and **methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-propionate** (Ih), were synthesized from the parent acids, Ie and Ig, following a published procedure.[82] If was obtained as a waxy solid (mp 59.2–60.0 °C) which could not be recrystallized, and Ih was obtained as white crystals after recrystallization from hexane/methylene chloride (mp 107.5–108.5 °C). Both compounds showed only one spot on TLC. Compounds prepared by published methods were **6-hydroxy-2-methoxy-2,5,7,8-tetramethylchroman** (Ij),[83] **4-methoxy-2,6-dimethylphenol** (VIa),[84] and **4-methoxytrimethylphenol** (VIb).[84] These compounds all had melting points in satisfactory agreement with their published values.[83,84]

6-Hydroxy-2,2,5,7,8-pentamethyl-2*H*-chromene (IIa), 4.0 g of Ib (18 mmol), 8.5 mL of acetic anhydride (90 mmol), and 3.75 g of sodium acetate (40 mmol) were heated at 100 °C for 30 min. The mixture was poured into 100 g of ice water and stirred for 1 h. The precipitate was filtered, washed with water, and dried under high vaccum for 12 h to yield 4.8 g of **6-acetoxy-2,2,5,7,8-pentamethylchroman** (Ik; 100%). Ik was converted into **6-acetoxy-2,2,5,7,8-pentamethyl-2*H*-chromene** (IIc) following the published procedure[85] for synthesizing 3,4-dehydro-α-tocopherol from α-T. 2,3-Dichloro-5,6-dicyanobenzoquinone (4.83 g, 21.2 mmol) was added in portions over 4 h to 4.8 g of Ik (18 mmol) in 120 mL of toluene at 120 °C under an atmosphere of nitrogen. The reaction was maintained at this temperature for 12 h after addition was complete. The mixture was cooled to 5 °C and filtered. The filtrate was evaporated and the residue subjected to "flash" chromatography[81] on silica gel with 5% ethyl acetate in hexane (v/v) as eluent. IIc was obtained as an oil which crystallized on standing (2.37 g; 49%). IIc (1.34 g, 5 mmol) in 13 mL of diethyl ether was added dropwise to a stirred suspension of 0.88 g of lithium aluminum hydride (23 mmol) in 13 mL of diethyl ether at room temperature. The mixture was stirred for 30 min. Moist ether was added to decompose the catalyst, followed by 18 mL of 1 N sulfuric acid. The reaction product was extracted into ether and the ether layer washed successively with water, sodium bicarbonate solution, and finally water. The ether extract was dried over sodium sulfate and evaporated to give 0.6 g of IIa (54% after one recrystallization from *n*-hexane, mp 70.3–71.8 °C): ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6, alkyl CH_3), 2.20 (s, 9, aromatic CH_3), 4.25 (s, 1, OH), 5.52 (d, J = 10 Hz, 1, vinyl H), 6.40 (d, J = 10 Hz, 1, vinyl H), Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31. Found: C, 76.85; H, 8.13.

2,3-Dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran (IIIb) was prepared by following the published procedure for the synthesis of IIId.[86] Trimethylhydroquinone (Aldrich; 0.1 mol) and 2-methyl-2-propen-1-ol (Aldrich; 0.1 mol) were refluxed for 48 h in anhydrous formic acid (400 mL, prepared by heating for 2 h with an excess of phthalic anhydride, followed by fractional distillation) containing 20 drops of concentrated sulfuric acid. The reaction mixture was poured on ice and extracted with ether (2 × 300 mL). The ether extract was washed with water (2 × 300 mL), aqueous sodium bicarbonate (2 × 300 mL), and saturated aqueous sodium chloride (300 mL) and dried over sodium sulfate. The residue obtained after evaporation of the ether was refluxed for 15 min in methanol (300 mL) containing concentrated hydrochloric acid (3 mL). The cooled reaction mixture was treated with methylene chloride (500 mL) and filtered to remove unreacted trimethylhydroquinone. The filtrate was washed with aqueous sodium bicarbonate (100 mL), water (100 mL), and saturated aqueous sodium chloride (100 mL) and dried over sodium sulfate. The residue obtained after evaporation was purified by flash chromatography on silica gel with 3% ethyl acetate in *n*-hexane and finally recrystallized from aqueous methanol to give fluffy, white crystals (2.5 g; 12% yield): mp 122–123 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6 H, alkyl CH_3), 2.15 (s, 9 H, aromatic CH_3), 2.87 (s, 2 H, CH_2), 4.15 (s, 1 H, OH). The NMR assignments agree well with the published data for IIId.[86] GC–MS of the trimethylsilyl ether gave the correct parent ion at 278 daltons. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.86; H, 8.85.

1,2,3,4-Tetrahydro-6-hydroxy-5,7,8-trimethylquinoline (IVa) was prepared by modifying an earlier, published procedure.[87] Trifluoroacetic

(78) α-Tocopheroxyl has, in fact, been reported to dimerize at low temperatures.[60]

(79) Dobson, G.; Grossweiner, L. I. *Trans. Faraday Soc.* **1965**, *61*, 708–714.
(80) Griva, A. P.; Denisov, E. T. *Int. J. Chem. Kinet.* **1973**, *5*, 869–877.
(81) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(82) Cohen, N.; Banner, B. L.; Neukom, C. *Synth. Commun.* **1982**, *12*, 57–65.
(83) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290–305.
(84) John, W.; Rathmann, F. H. *Chem. Ber.* **1940**, *73*, 995–1001.
(85) Mayer, H.; Isler, O. In "Methods in Enzymology"; McCormick, D. B.; Wright, L. D., Eds.; Academic Press: New York, 1971; Vol. 18, Part C, pp 241–348.
(86) Lars, J.; Nilsson, G.; Selander, H.; Sievertsson, H.; Skånberg, I. *Tetrahedron* **1970**, *26*, 879–886.

acid (3.8 mL, 50 mmol) was added to a suspension of 10 g of 6-hydroxy-5,7,8-trimethylquinoline[87] (53 mmol) in 200 mL of methanol. The resulting solution was hydrogenated at 40 psi for 2.5 h in the presence of platinum oxide (1 g). After this time, the mixture was filtered through Celite and the filtrate evaporated to yield 13.9 g of 6-hydroxy-5,7,8-trimethylquinolinium trifluoroacetate (87%; mp >300 °C). The quinolinium trifluoroacetate salt (7 g) was suspended in 140 mL of 95% ethanol and 35 mL of a saturated sodium bicarbonate solution was added, followed by 140 mL of water. After partial evaporation and cooling of the solution a precipitate formed which was filtered off and dried under high vacuum for 12 h to give 4.1 g of IVa (93%). Recrystallization from ethyl acetate gave pale brown crystals, mp 132.7–132.9 °C (lit.[87] mp 128–131 °C), which turned darker brown over a period of days.

1-Acetyl-1,2,3,4-tetrahydro-6-hydroxy-5,7,8-trimethylquinoline (IVb) was prepared from IVa by the method reported in the literature.[87]

1-Ethyl-1,2,3,4-tetrahydro-6-hydroxy-5,7,8-trimethylquinoline (IVc). A solution of 4.1 g of IVb (20 mmol) in 20 mL of dry tetrahydrofuran was added dropwise to a suspension of 1.6 g of lithium aluminum hydride (42 mmol) in 20 mL of the same solvent, while maintaining a gentle reflux. The mixture was refluxed for a further hour after the addition was complete. The reaction mixture was then cooled in ice and 50 mL of a solution of ethyl acetate in tetrahydrofuran (1:1 (v/v)) was slowly added dropwise. This was followed by the addition of 50 mL of ethyl acetate and finally 150 mL of 3 M HCl. The milky suspension was separated and a saturated solution of sodium bicarbonate was added slowly, with stirring and cooling at 5 °C, to the aqueous fraction. The suspension was then extracted with ethyl acetate (2 × 250 mL) and the ethyl acetate extract washed with saturated sodium chloride solution (1 × 50 mL) and dried over sodium sulfate. Evaporation of the ethyl acetate gave a white precipitate which was recrystallized from hot *n*-heptane and ethyl acetate to give 1.0 g of IVc (25%; mp 141.4–141.6 °C): ^{1}H NMR ($(CD_3)_2SO$) δ 1.15 (t, J = 7 Hz, 3, ethyl CH_3), 1.5–1.8 (m, 2, ring CH_2), 1.90 (s, 3, aromatic CH_3), 2.10 (s, 6, aromatic CH_3), 2.45 (m, 4, ring CH_2 and *N*-ethyl CH_2), 2.7–3.0 (m, 2, benzylic CH_2). Anal. Calcd for $C_{14}H_2NO$: C, 76.66; H, 9.65; N, 6.38. Found: C, 76.49; H, 9.57; N, 6.44.

3,4-Dihydro-6-hydroxy-4,4,5,7,8-pentamethyl-2*H*-1-(benzothio)pyran (V). 4-Mercaptotrimethylphenol[42] (1.1 g, 6.5 mmol), 12 mL of anhydrous formic acid, and 1.0 mL of 3-methyl-2-buten-1-ol (9.8 mmol) were refluxed under argon for 2 h. The reaction mixture was cooled to 5 °C, diluted with 20 mL of water, and extracted with ether (3 × 25 mL) and the combined ether layer washed with cold 1 M sodium hydroxide solution. The separated ether fraction was dried over sodium sulfate and the ether was removed by evaporation. The brown oil obtained was gently refluxed for 1 h with 12 mL of 6% methanolic potassium hydroxide under argon. The cooled solution was diluted with 20 mL of water and extracted with ether (3 × 25 mL). The combined ether extracts were washed with water (2 × 15 mL) and dried over sodium sulfate and the ether removed to give 0.9 g of a brown resin. This residue was subjected to careful medium-pressure chromatography on silica gel with 5% ethyl acetate in hexane (v/v). A yellow oil was obtained as the main fraction (0.52 g) which, after trituration with *n*-hexane and standing overnight at 0 °C, yielded 0.1 g of colorless crystals of V. The remaining yellow oil resisted all attempts at further crystallization. The crystalline material was recrystallized from *n*-hexane (mp 86.4–87.3 °C). ^{1}H NMR (at 80 MHz in $CDCl_3$) δ 1.45 (s, 6, $C(CH_3)_2$), 1.87–2.13 (m, 2, CH_2), 2.13 (s, 3, aromatic CH_3), 2.25 (s, 3, aromatic CH_3), 2.42 (s, 3, aromatic CH_3), 2.75–3.00 (m, 2, CH_2), 4.50 (s, 1, OH). Anal. Calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53. Found: C, 70.49; H, 8.66. X-ray diffraction analysis confirmed the assigned structure.

Measurement of k_1 Values by the IAS Method. Oxygen uptake was monitored essentially as described before[3b] with a more sensitive pressure transducer (Validyne, Northridge, Calif.; 65 torr full-scale) with use of (a) 25 mM AIBN in 7.0 mL of vacuum-distilled styrene and 1.0 mL of chlorobenzene for the more reactive antioxidants or (b) 20 mM AIBN in 1 mL of styrene and 1 mL of chlorobenzene for the less reactive compounds. The k_1 values were determined from the averaged product of the slope, $d[O_2]/dt$, and the projected, remaining induction period, τ, at several points on the inhibited oxidation curve (for inhibited rates less than 10% of the final, uninhibited rate) by using the fact that $(d[O_2]/dt)\tau = k_2[\text{styrene}]/k_1$ = a constant. The k_1 value relative to α-tocopherol was obtained directly by taking the ratio of the $((d[O_2]/dt)\tau)$ product. Absolute values of k_1 could then be calculated by using the k_1 value for α-tocopherol (determined many times) or by using the calibration factor for the apparatus (and reaction flask) together with the known value for k_2 and the concentration of styrene.

Measurement of k_1 Values by the LKEPR Method. Small quantities of the phenol were dissolved in a mixture of di-*tert*-butyl ketone (0.90 M) and cyclopentane or *n*-decane and the solution was saturated with O_2 at 760 torr by bubbling for 10–20 min. The phenol concentration was in the range 2×10^{-5} to 6×10^{-4} M depending upon its reactivity. For all of the more reactive phenols a flow system was employed. These solutions were subjected to the pulse from a nitrogen laser (337 nm, ~8 ns, up to 10 mJ/pulse) while flowing through the cavity of a Varian E 104 EPR spectrometer at a temperature of 24 °C. Since the highly reactive phenols were used at rather low concentrations, it was necessary to replace the portion of the sample photolyzed by fresh solution after each light pulse in order to prevent excessive depletion of the phenol. The decay of the EPR signal due to the $Me_3COO\cdot$ and $Me_3CC(O)OO\cdot$ radicals was monitored at a fixed magnetic field. Interference with the peroxyl decay trace from the "grow-in" of the phenoxyl signal was avoided by working on the low-field tail of the peroxyl signal (3215 G at 9.13 GHz) under conditions of high modulation amplitude (8 G) and high microwave power (100 mw).[88] Up to 140 individual decay traces were collected and averaged on a Nicolet 1170 signal averager. Values of k_1 were calculated as described in the Results Section.

X-ray diffraction. These studies were performed with an automatic 4-circle Picker diffractometer by the $\theta/2\theta$ scan method with line profile analysis.[89] The cell parameters were obtained by least-squares refinement of the setting angles of reflections with large 2θ values. Structures were determined for compounds Ic, IIb, IIId, and V. Compound Ic was recrystallized from hexane–methylene chloride, compound IIb from aqueous ethanol, and compound V from hexane, and compound IIId was used as received. The structures were solved with the direct methods program MULTAN[90] and refined by block diagonal least squares with counting statistics weights. Scattering curves for neutral atoms were taken from the literature,[91] and an extinction correction[92] was included in the calculations which were performed with use of the NRC PDP8-E system of programs.[93] Details of space group, unit cell, data collection, and residuals are given in Table VI of the Supplementary Material.

EPR Spectra. Solutions of the phenols (ca. 5×10^{-2} M) in benzene/di-*tert*-butyl peroxide (5:1 (v/v)) were degassed and sealed under vacuum in quartz EPR cells. Phenoxyl radicals were generated by continuous low-intensity UV irradiation of the sample tube in the cavity of a Varian E104 EPR spectrometer at room temperature. The spectrum of the radical derived from **Ia** was obtained in the same general way, the precise experimental conditions being described in the caption to Figure 3. EPR parameters were determined with the aid of a Varian NMR Gauss meter and a microwave frequency meter (Autohet Counter Model 350 D) with use of the tetracene radical cation (g = 2.002604) as a reference for the g values and comparison with computer-simulated spectra for the hyperfine splittings.

Phenoxyl Radical Decay Kinetics. Phenoxyl radicals were generated essentially instantaneously by a brief flash of intense UV irradiation of a sample containing ca. 5×10^{-2} M phenol in benzene/di-*tert*-butyl peroxide (10:1 (v/v)). These solutions either were sealed under vacuum or were continuously saturated with oxygen at a pressure of 760 torr. Decay of the phenoxyl radicals was monitored at a fixed magnetic field which was preset to the main peak in the phenoxyl spectrum. Phenoxyl radical concentrations were determined by comparison with a standard solution of diphenylpicrylhydrazyl in the usual way.[94]

Acknowledgment. This work was supported by a grant from the National Foundation for Cancer Research and the International Association for Cancer Research. We also thank Drs. N. Cohen, J. W. Scott, and L. H. Sutcliffe for generous samples of some of the phenols used in this work and for helpful advice on synthesis.

Registry No. Ia, 21704-70-1; Ib, 950-99-2; Ic, 56305-04-5; Id, 86646-83-5; Ie, 86646-84-6; If, 98760-49-7; Ig, 4072-32-6; Ih, 98760-50-0; Ii, 79907-49-6; Ij, 98777-24-3; Ik, 57721-81-0; IIa, 56306-89-9; IIb,

(87) Svensson, K. G.; Nilsson, J. L. G. *Acta Pharm. Suecc.* **1973**, *10*, 277–284.

(88) Peroxyl radicals do not saturate readily, see: Thomas, J. R. *J. Am. Chem. Soc.* **1966**, *88*, 2064–2065.

(89) Grant, D. F.; Gabe, E. J. *J. Appl. Crystallogr.* **1978**, *11*, 114–120.

(90) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368–376.

(91) "International Tables for X-ray Crystallography"; Kynoch Press: Birmingham, England, 1974; Vol. 4.

(92) Larson, A. C. In "Crystallographic Computing"; Ahmed, F. R., Ed.; Munksgaard: Copenhagen, 1970; p 291.

(93) Larson, A. C.; Gabe, E. J. *Comput. Crystallogr. Proc. Int. Summer Sch.* **1978**, 81–89; edited by Schenk, H., Olthof-Hazekamp, R., Van Koningsveld, H. Delft University Press: Delft, Netherlands.

(94) Adamic, K.; Dunn, M.; Ingold, K. U. *Can. J. Chem.* **1969**, *47*, 287–294.

98760-51-1; IIc, 93159-17-2; IIIa, 86646-86-8; IIIb, 84574-05-0; IIIc, 87207-96-3; IIId, 26172-18-9; IVa, 50869-01-7; IVb, 50869-02-8; IVc, 86646-85-7; V, 98760-52-2; VIa, 2431-91-6; VIb, 53651-61-9; VIc, 19587-93-0; VId, 2819-86-5; VIe, 3238-38-8; VIf, 527-60-6; VIg, 527-35-5; VIh, 576-26-1; VIIa, 489-01-0; VIIb, 128-37-0; VIIc, 128-39-2; δ-T, 119-13-1; γ-T, 54-28-4; β-T, 16698-35-4; α-T, 59-02-9; DMT, 17976-95-3; 2-methyl-2-propen-1-ol, 513-42-8; 6-hydroxy-5,7,8-trimethylguinoline, 50869-00-6; 6-hydroxy-5,7,8-trimethyltetrahydroquinolinium trifluoroacetate, 98760-53-3; 4-mercaptotrimethylphenol, 85460-73-7; 3-methyl-2-buten-1-ol, 556-82-1; trimethylhydroquinone, 700-13-0; styrene, 100-42-5.

Supplementary Material Available: Tables VI–XXI giving detailed X-ray crystallographic data, final parameters, and structural factor lists (70 pages). Ordering information is given on any current masthead page.

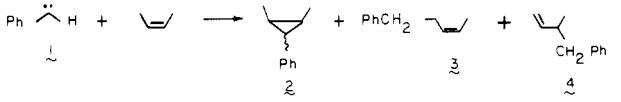
The Formation of an Enantiomerically Pure Product of Free Radical Coupling. The Chemistry of Diphenylcarbene in Polycrystalline (*S*)-(+)-2-Butanol[1]

José Zayas and Matthew S. Platz*[2]

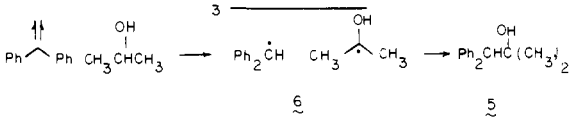
Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received February 19, 1985*

Abstract: Photolysis of 0.1 M diphenyldiazomethane at 77 K or 137 K in solid (*S*)-(+)-2-butanol gives tertiary alcohol **9** along with other products. Compound **9** was isolated and found to be enantiomerically pure by chiral NMR shift reagents. Compound **9** is formed by reaction of triplet diphenylcarbene with (*S*)-(+)-2-butanol to give a radical pair which subsequently collapses. The solid-state matrix directs the radical pair collapse with complete retention of configuration.

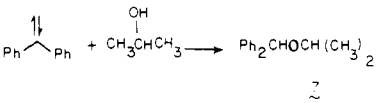
In 1971 Moss and Dolling discovered that the photochemical generation of arylcarbenes in low-temperature solids enhances the yield of triplet-derived products.[3] Phenylcarbene **1** reacts with *cis*-2-butene in solution to give >85% of cyclopropanes **2** (syn and anti) and only a small (<15%) amount of olefins **3** and **4**. In the solid state (−196 °C) the yield of **3** plus **4** exceeds 50% and the yield of **2** drops below 50%.



In subsequent years several more examples of the unusual solid-state chemistry of arylcarbenes have been reported by Moss,[4] Tomioka,[5] and Platz.[6] Tomioka discovered that diphenylcarbene (DPC) reacts with 2-propanol in the solid state to give high yields of alcohol **5**, presumably by hydrogen atom abstraction by triplet DPC to give radical pair **6**. In solution phase only trace amounts



of **5** are formed, the near exclusive product being ether **7** derived from reaction of singlet DPC with solvent. It occurred to us that



if a chiral alcohol were employed as a polycrystalline matrix then a radical pair (such as **6**) would again be formed. The rigid polycrystalline environment should prevent rotational motion of the components of the radical pair and direct their collapse to form a stable product in only one sense to give an enantiomerically enriched material. As described in the next section these expectations were confirmed in the diphenylcarbene–2-butanol system.

Table I. Absolute Yield (±2%) of Products Formed by the Reaction of DPC with D,L-2-Butanol and (*S*)-(+)-2-Butanol at 77 K

	absolute yield (%)	
product	D,L-2-butanol	(*S*)-(+)-2-butanol
8	6	6
9	12	13
10	5	6
11	1	1
12	1	1
13	11	10
total	36	37

Table II. Absolute Rate of Decay of Triplet DPC in D,L- and (*S*)-(+)-2-Butanol at 98 K (Three Trials Each)

D,L k ($s^{-1/2}$)	(*S*)-(+) k ($s^{-1/2}$)
2.96×10^{-2}	2.69×10^{-2}
2.73×10^{-2}	2.50×10^{-2}
2.60×10^{-2}	2.80×10^{-2}
av $2.8 \pm 0.2 \times 10^{-2}$	av $2.7 \pm 0.2 \times 10^{-2}$

Results

The DPC–2-butanol system was chosen based upon Tomioka's results and the accessibility of enantiomerically pure (*S*)-(+)-2-

(1) A portion of this work has been published in preliminary form: Zayas, J.; Platz, M. S. *Tetrahedron Lett.* **1983**, *24*, 3689.
(2) Alfred P. Sloan Fellow and Camille and Henry Dreyfuss Teacher Scholar.
(3) Moss, R. A.; Dolling, U.-H. *J. Am. Chem. Soc.* **1971**, *93*, 954.
(4) (a) Moss, R. A.; Joyce, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 1262; **1977**, *99*, 7399. (b) Moss, R. A.; Huselton, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 1314. (c) Moss, R. A.; Wetter, W. P. *J. Am. Chem. Soc.* **1981**, *22*, 997.
(5) (a) Tomioka, H.; Griffin, G. W.; Nishiyama, K. *J. Am. Chem. Soc.* **1979**, *101*, 6009. (b) Tomioka, H.; Ozaki, Y.; Koyabu, Y.; Izawa, Y. *Tetrahedron Lett.* **1982**, *23*, 1917. (c) Tomioka, H.; Suzuki, S.; Izawa, Y. *Chem. Lett.* **1980**, 293. (d) Tomioka, H.; Ozaki, Y.; Izawa, Y. *Chem. Lett.* **1982**, 843. (e) Tomioka, H.; Izawa, Y.; *J. Am. Chem. Soc.* **1977**, *99*, 6128. (f) Tomioka, H. *J. Am. Chem. Soc.* **1979**, *101*, 256. (g) Tomioka, H.; Miwa, T.; Suzki, S.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 753. (h) Tomioka, H.; Okuno, H.; Izawa, Y. *J. Chem. Soc., Perkin Trans. 2* **1980**, 603. (i) Tomioka, H.; Itoh, M.; Yamakawa, S.; Izawa, Y. *J. Chem. Soc., Perkin Trans. 2* (1980), 1636.
(6) (a) Palik, E. C.; Platz, M. S. *J. Org. Chem.* **1983**, *48*, 963. (b) Reference 1. (c) Tomioka, H.; Hayashi, N.; Izawa, Y.; Senthilnathan, V. P.; Platz, M. S. *J. Am. Chem. Soc.* **1983**, *105*, 5053.

0002-7863/85/1507-7065$01.50/0