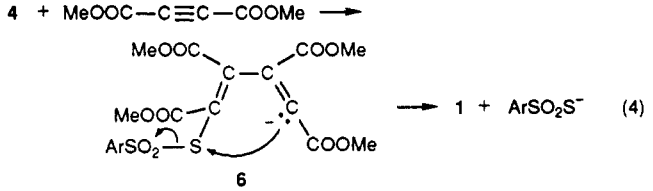
postulated[9] to under go 1,3-dipolar addition to acetylenes to form thiophenes (eq 3b).[10] Another option (eq 4) would have 4 react reversibly with a second alkyne to give 6, which would then cyclize to the thiophene.



Experimental Section

Reactions with Dimethyl Acetylenedicarboxylate. Potassium *p*-toluenethiosulfonate (1.13 g, 5 mmol) was added slowly to a stirred solution of 1.42 g (10 mmol) of dimethyl acetylenedicarboxylate (Aldrich) in 20 mL of acetonitrile. The reaction mixture was stirred at room temperature for 2 h and then poured into water. The product was extracted with methylene chloride. The methylene chloride extracts were dried ($MgSO_4$), and the organic solvent was removed by evaporation. The residue was purified by chromatography on silica gel using 1:2 CH_2Cl_2–hexane as eluant. Recrystallization from methanol gave 1.20 g (76%) of tetramethyl thiophenetetracarboxylate (1), mp 124–125 °C (lit.[2] mp 125 °C); ^1H NMR ($CDCl_3$) δ 3.92; IR (KBr) 2960, 1720, 1540, 1440, 1270, 1220, and 1000 cm^{-1}.

Potassium thiocyanate (0.97 g) was added to a stirred solution of 1.42 g of dimethyl acetylenedicarboxylate in 20 mL of acetonitrile, and the reaction mixture was stirred at room temperature for 5 h. It was then worked up in the same manner as in the reaction with p-$CH_3C_6H_4SO_2SK$. The products were separated by column chromatography on silica gel using 1:1 CH_2Cl_2–hexane as the eluant. After recrystallization from methanol there was obtained 0.30 g (19%) of 1, mp 124–125 °C, and 0.88 g (44%) of thiocyanate 2: mp 34–35 °C; ^1H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 3.97 (s, 3 H), 6.88 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.66, 53.83, 108.29, 125.97, 137.82, 161.54, 164.57. Anal. Calcd for $C_7H_7NO_4S$: C, 41.79; H, 3.51; N, 6.96. Found: C, 41.86; H, 3.59; N, 6.83.

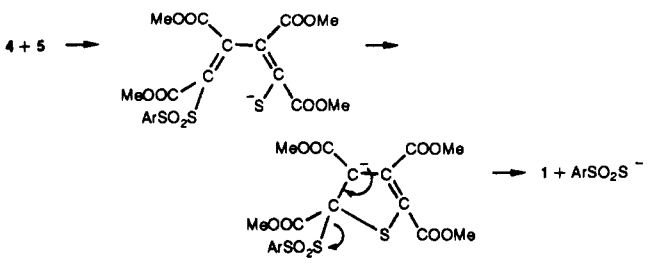
Potassium Selenocyanate. Reaction of KSeCN (0.72 g, 5 mmol) with dimethyl acetylenedicarboxylate (1.42 g, 10 mmol) was carried out in the same manner as with KSCN. After workup and chromatography on silica gel using 1:2 CH_2Cl_2–hexane as eluant there was obtained 0.86 g (49%) of selenocyanate 3: mp 40–41 °C; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3 H), 3.96 (s, 3 H), 6.95 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 53.89, 53.92, 120.55, 122.78, 143.39, 163.44, 167.54. Anal. Calcd for $C_7H_7NO_4Se$: C, 33.89; H, 2.84. Found: C, 33.47, H, 2.88.

Reactions with Ethyl 3-Phenyl-2-propynoate. Potassium *p*-Toluenethiosulfonate. Ethyl 3-phenyl-2-propynoate (1.74 g, 10 mmol) and p-$CH_3C_6H_4SO_2SK$ (1.13 g, 5 mmol) were added to 20 mL of acetonitrile, and the reaction mixture was stirred at reflux for 14 days. It was then worked up in the same manner as in the other reactions. The residue remaining after the removal of the methylene chloride was recrystallized from methanol giving 1.26 g (76%) of ethyl 3-(*p*-tolylsulfonyl)-3-phenyl-2-propenoate: mp 83–84 °C; ^1H NMR ($CDCl_3$) δ 1.03 (t, 3 H), 2.40 (s, 3 H), 4.00 (q, 2 H), 7.01–7.48 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 13.62, 21.59, 61.19, 126.77, 127.72, 129.04, 129.31, 129.52, 129.62, 129.89, 134.16, 145.03, 154.54, 163.77; IR (KBr) 3000, 1730, 1600, 1315 (SO_2), 1210, 1145 (SO_2) cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49. Found: C, 65.04; H, 5.46.

Sodium *p*-Toluenesulfinate. Stirring a mixture of 0.45 g (2.5 mmol) of sodium p-toluenesulfinate and 0.41 g (2.5 mmol) of ethyl 3-phenyl-2-propynoate in 20 mL of acetonitrile under reflux for 40 h gave upon workup 0.60 g (73%) of ethyl 3-(*p*-tolylsulfonyl)-3-phenyl-2-propenoate, mp 83–84 °C.

(9) Benitez, F. M.; Grunwell, J. R. *Tetrahedron Lett.* **1977**, 3413.

(10) It is also possible that 5 might give 1 by reacting with a second 4 via the sequence shown below:



Development of Novel Phenolic Antioxidants. Synthesis, Structure Determination, and Analysis of Spiro[2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuran-2,1′-cyclopropane]

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Received April 6, 1992

Introduction

Sterically hindered phenols form an important class of peroxyl trapping antioxidants. Indeed, α-tocopherol (**1a**), a component of vitamin E, is the major lipid-soluble antioxidant in human blood,[1] and its biological function, as well as that of analogs of it, continues to be of considerable interest.[2] Ingold and co-workers have published a number of papers defining the structural features that are responsible for the high antioxidant activity of 1 and its analogs, at least as measured in homogeneous solution,[3] and they and others[4] have determined rate constants, k_1, for the reaction of the phenols with peroxyl radicals (eq 1). Complementary studies have been reported in micellar

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

systems[5] and more recently in environments designed to model biological membranes.[2]

The relative efficacies of the phenolic antioxidants, as reflected in k_1, as well as the absolute values of these rate constants are found to be media dependent.[6] It is clear that the major factor defining the free radical chain terminating activity of the phenols is the nature of the substitution on the aromatic ring, as shown by the data compiled in Table I. Ortho, meta, and para alkyl, para alkoxy, and alkylthio groups are seen to augment the reactivity of the phenols toward radicals, owing to stabilization of the incipient phenoxyl radical character of the transition state for hydrogen atom transfer.[3d,e,4] EPR studies have

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

(2) See, e.g.: (a) Serbinova, E.; Kagan, V.; Han, D.; Packer, L. *Free Radicals Biol. Med.* **1991**, *10*, 263–275. (b) Barclay, L. R. C.; Baskin, K.; Dakin, K. A.; Locke, S. J.; Vinqvist, M. R. *Can. J. Chem.* **1990**, *68*, 2258–2269.

(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. (c) Burton, G. W.; Hughes, L.; Ingold, K. U. *Ibid.* **1983**, *105*, 5950–5951. (d) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *Ibid.* **1985**, *107*, 7053–7056. (e) Zahalka, H. A.; Robillard, B.; Hughes, L.; Lusztyk, J.; Burton, G. W.; Janzen, E. G.; Kotake, Y.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 3739–3745.

(4) Burkalova, Ye. B.; Kuchtina, Ye. E.; Ol'khovskaya, I. P.; Sarycheva, I. K.; Sinkina, Ye. B.; Kharapova, N. G. *Biofizika* **1980**, *24*, 989–993.

(5) Castle, L.; Perkins, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 6381–6382. Pryor, W. A.; Strickland, T.; Church, D. F. *Ibid.* **1988**, *110*, 2224–2229. Barclay, L. R. C.; Baskin, K. A.; Locke, S. J.; Schaffer, T. D. *Can. J. Chem.* **1987**, *65*, 2529–2250.

(6) This subject is summarized in ref 2b.

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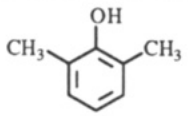
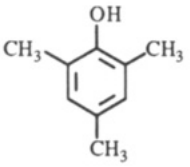
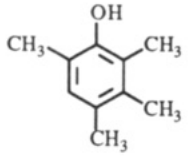
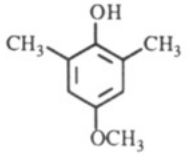
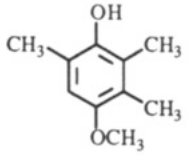
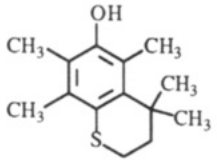
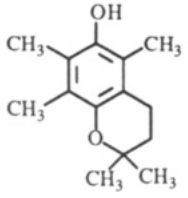
Table I. A Selection of Rate Constants for H-Atom Transfer from Phenols to Polystyrylperoxyl Radical[a]

substrate	10^4k_1 (M^{-1} s^{-1})	k_{rel}
	2.5	1.0
	8.5	3.4
	11	4.4
	94	38
	130	52
	280	112
	380	152

[a] Taken from ref 3d.

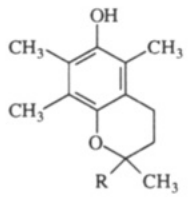
confirmed that the heteroatom-containing substituents interact with the unpaired spin in the phenoxyls.[3d,e] Moreover, stereoelectronic effects appear to be important in the case of alkoxy[3d] and alkylthio[3e] groups. For example, k_1 for **1a** is 8.2 times that for the analog, 2,3,5,6-tetramethyl-4-hydroxyanisole (**2**).[3d] This difference is ascribed to steric factors in **1** that limit the dihedral angle, Θ, as shown in the Newman projection **3**, to values near the ideal of 0°, the angle at which the overlap between a nonbonding 2p-type pair of electrons on the oxygen atom and the π-system of the aromatic ring is optimized. Consistent with this proposition is the fact that the value of Θ for **1b**, a close analog of α-tocopherol (**1a**), is found to be 17°, whereas steric repulsions between ring methyl groups and that of the methoxy function in **2** force an increase in the critical dihedral angle, Θ, to 90°. Additional support for the hypothesis of this type of stereoelectronic effect has been claimed by the finding that in homogeneous solution the

Table II. Calculated and Experimental Parameters for 4 and 5

entry	4	5
1 Θ_1 (calcd) (C–O–C_{Ar}–C_{Ar})	0.3°,[a] 0.2°,[b] 4.9°[c]	0.0°,[a] 0.2°,[b] 1°[c]
2 Θ_1 (expl) (C–O–C_{Ar}–C_{Ar})[d]	12.0°	9.0°[e]
3 $\Theta_{(calcd)}$ (H–O–C_{Ar}–C_{Ar})	19.7°,[a] 11.4°,[b] 8.1°[c]	9.2°,[a] 2.6°,[b] 2.5°,[c] 95.6°[f]
4 $\Theta_{(expl)}$ (H–O–C_{Ar}–C_{Ar})[d]	27.8°	90.0°[e]
5 BDE (kcal/mol)	81.8°[a]	82.6°[a]
6 ionization potential[a] (eV)	8.33	8.36
7 $E_{p/2}$[g] (mV)	675 ± 15[h]	738 ± 8
8 10^4k_1 (M^{-1} s^{-1})	570 ± 57[3d]	379 ± 82

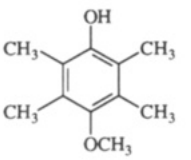
[a] Value computed by AM1. [b] Value computed by PM3. [c] Value computed by MMX. [d] Values obtained from single-crystal X-ray crystallographic analysis. [e] Value for *O-tert*-butyldimethylsilyl derivative. [f] Value computed by MMX for *O-tert*-butyldimethylsilyl derivative. [g] vs SCE. Chart speed of 50 mV/s. [h] A value of $E_{p/2}$ = 810 mV (vs SCE) has been reported, but the chart speed was not stated: Mukai, K.; Okabe, K.; Hosose, H. *J. Org. Chem.* **1989**, *54*, 557–560.

dihydrofuran **4** quenches peroxyl radicals 1.5 times more rapidly than does **1b**;[3e] although the X-ray crystal structure of **4** was not obtained, analysis of models led the authors to conclude that the greater rigidity restricted this molecule to a geometry in which Θ is less than 17°.

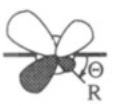


1a. R = $C_{16}H_{33}$

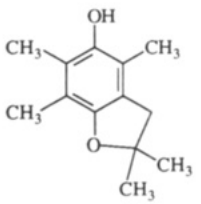
1b. R = CH_3



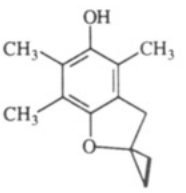
2



3



4



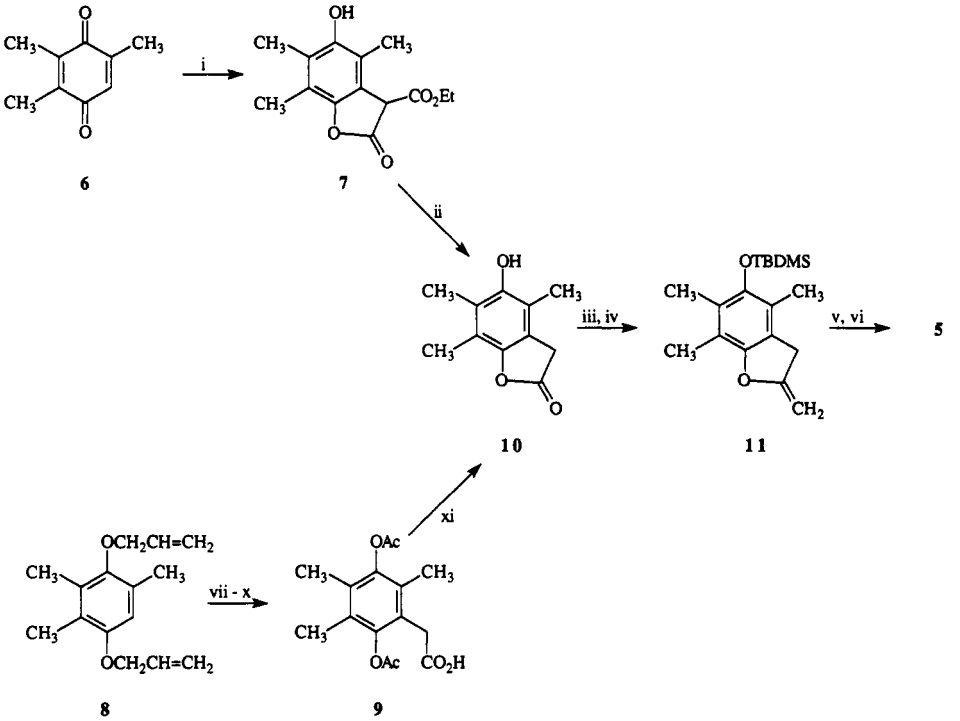
5

In considering possible modifications of **4** that might foster even greater efficacy of such phenols as antioxidants, we speculated that conversion of the geminal dimethyl group to a spirocyclopropyl moiety would flatten the five-membered ring further, giving a yet smaller value of Θ. We also thought that this transformation might increase the electronic delocalization of the phenoxyl radical derived from it, owing to the known modest ability of cyclopropyl rings to stabilize radicals α to the ring[7] and thus improve the chain-terminating properties of the molecule.

In this paper we report theoretical studies of **4** and **5**, key parameters of their X-ray crystal structures, and experimental results that allow comparison of their antioxidant abilities.

(7) (a) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687–5698. (b) Bauld, N. L.; McDermed, J. D.; Hudson, C. E.; Rim, Y. S.; Zoeller, J., Jr.; Gordon, R. D.; Hyde, J. S. *J. Am. Chem. Soc.* **1969**, *91*, 6666–6676.

Scheme I. Synthesis of 5[a]



[a] Key: i. $NaCH(CO_2Et)_2$/EtOH (93%); ii. DMSO, 110–120 °C (99%); iii. TBDMSCl/imidazole/THF (100%); iv. Tebbe's reagent/THF, 0 °C (50%); v. $CH_2I_2/ZnEt_2/Et_2O$ (93%); vi. n-$Bu_4N^+F^-$/THF (92%); vii. BCl_3/CH_2Cl_2, −70 °C to rt (87%); viii. Ac_2O/Pyr (82%); ix. O_3/CH_3OH, −78 °C then $(CH_3)_2S$, −78 °C to rt (85–98%); x. CrO_3/H_2SO_4 (88%); xi. K_2CO_3/CH_3OH then HCl (98%).

Results and Discussion

A. Theoretical Calculations. The ground-state geometries of **4** and **5** were calculated using the techniques of AM1,[8] its PM3 modification,[9] and MMX,[10] and the resulting structural data most relevant to predicting the relative H-atom donating abilities of the two phenols are contained in Table II. With respect to the key dihedral angle, Θ, it can be seen that the AM1 method makes little distinction between **4** and **5**, both being close to or at the optimal angle of 0° (entry 1). Not surprisingly, a comparable prediction results from a PM3 calculation on these two phenols. The MMX calculation, in contrast, predicts that this angle will be 5° in **4** and 1° in **5**,[11] a result that suggests the latter substrate would be the better radical-chain terminator.

Consideration of a different dihedral angle, viz., that between the O-H bond of the phenol and the aromatic ring, leads to the opposite conclusion, however. At the transition state for transfer of the phenolic H-atom to an attacking radical, this angle optimally should be 90°, given the stereoelectronic requirements for delocalization of unpaired electron density into the aromatic ring.[12] As indicated by the data in Table II (entry 3), all three of the theoretical approaches that we used predict the relevant dihedral angle in **4** to be greater than that in **5**, although in no case does this angle exceed 20°. If these calculated differences in ground-state geometries affect the relative energies of the transition states for H-atom abstraction, these data would point to **4** as the better inhibitor.[13]

Comparison of the O–H bond dissociation energies (BDE) and the ionization potentials of **4** and **5** using semiempirical techniques was also performed in order to assess the effect of the spirocyclopropyl moiety. The latter values are of interest because ionization and oxidation potentials are linearly correlated in organic molecules,[14] and others have shown that there is also a linear correlation between the oxidation potentials of phenols and the rate constant for transfer of the phenolic hydrogen atom to peroxyl radicals.[15] The BDEs were taken as the difference in the heat of the reaction between the respective phenol and hydrogen atom to afford dihydrogen and the corresponding phenoxy radicals (eq 2), structures of which were

$$ArOH + H^\bullet \rightarrow ArO^\bullet + H_2 \qquad (2)$$

optimized with AM1. The parameters relevant to the desired comparison between **4** and **5** are shown in Table II (entries 5 and 6). The calculated O–H BDEs are seen to be the same, within the error limits of the computational method used, as are the ionization potentials of the two compounds.

In summary, application of semiempirical and force-field computational techniques gives ambiguous results with respect to a prediction of the relative antioxidant abilities of phenols **4** and **5**. What does seem clear from the calculations is that the two phenols will be comparable as antioxidants. Experimental data were sought to assess the validity of this conclusion.

(8) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
(9) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209–220; *Ibid.* 220–264.
(10) Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. *Adv. Mol. Model.* **1990**, *2*, 65–92.
(11) A calculation using MM1 gives predicted angles of 10° and 5°, respectively, for **4** and **5**.
(12) Indeed, it has recently been shown that the ease of *benzylic* C–H abstraction by bromine atoms is optimized when this angle is 90°: Tanko, J. M.; Kamrudin, N.; Blackert, J. F. *J. Org. Chem.* **1991**, *56*, 6395–6399.
(13) The expectation that the ground-state geometries would carry over to the transition states is made somewhat tenuous by the anticipated low barrier to rotation about the C–OH bond.
(14) Miller, L. L.; Nordblom, G. D.; Mayeda, E. A. *J. Org. Chem.* **1972**, *37*, 916–918.
(15) Mukai, K.; Fukuda, K.; Tajima, K.; Ishizu, K. *J. Org. Chem.* **1988**, *53*, 430–432.

B. Synthesis of 5. The synthesis of the target compound **5** was readily accomplished by modified Simmons–Smith cyclopropanation[16] and deprotection of the enol ether **11**, itself drived from lactone **10** by silylation and reaction with Tebbe's reagent (Scheme I).[17] The proclivity of **11** to suffer isomerization to the corresponding benzofuran upon purification by column chromatography could be suppressed by using basic alumina saturated with triethylamine as the adsorbate.

The lactone **10** was prepared by two routes, as shown in Scheme I. The first, and simpler sequence, involved Michael addition of sodium malonate to 2,3,6-trimethyl-1,4-benzoquinone (**6**) to afford the lactone **7**.[18] This in turn was converted to **10** by heating in aqueous DMSO.[19] A more lengthy route to this lactone was devised in anticipation that geminal substitution at the benzylic position of the dihydrofuran moiety might ultimately be of interest. This sequence involved the Claisen rearrangement of the bis-allylated hydroquinone **8** as a key step, a transformation that was effected at low temperatures with the aid of boron trichloride; concommitant deallylation of the ortho-disubstituted oxygen atom occurred. The hydroquinone that resulted was protected by acetylation. Ozonolysis followed by oxidative workup (H_2O_2/HCO_2H) afforded the desired acid **9**, but in yields and purity that were low. An alternative sequence involving ozonolysis, reductive workup, and oxidation allowed isolation of **9** in excellent yields and purity, and this material was readily transformed to **10** by deprotection and lactonization.

C. Assessment of the Antioxidant Properties of 4 and 5. As a first experimental test of the theoretical predictions, the electrochemical oxidation of **4** and **5** was examined in acetonitrile. The process was found to be irreversible, and the half-peak oxidation potentials, $E_{p/2}$ (vs SCE), as determined by cyclic voltammetry, are given in Table II, entry 7. The values of 675 and 738 mV, respectively, are seen to be in the same order as the computed ionization potentials. This implies that **4** should be the better antioxidant. However, X-ray crystallographic analyses of **4** and of **5**, as its *tert*-butyldimethylsilyl ether,[20] show that the key dihedral angles are 12° and 9°, respectively, for the two compounds (Table II, entry 2),[21] indicative of a reverse ordering of antioxidant abilities.

Conclusive evidence for the relative reactivities of the two phenols toward peroxy radicals was obtained by measuring the rate constant for hydrogen atom abstraction according to the method of Ingold et al.[3d] As shown in entry 8 of Table II, the value for **5** is about 70% of that reported for **4**.[3d] Consequently, in homogeneous solution, phenol **4** is the superior antioxidant by a modest margin. Whether the same ordering of reactivities exists in media mimicking biological environments remains to be determined.

D. Conclusions. Incorporation of a spirocyclopropyl group α to an ethereal oxygen atom located in the para position of aromatic phenols, as in **5**, does not enhance antioxidant activity in homogeneous solution. This is in spite of the fact that this substituent appears to improve the stereoelectronic relationship between the nonbonding electrons on the ethereal oxygen atom and the π-system of the aromatic ring. MMX calculations correctly predict this improvement, whereas AM1 does not. Nevertheless, the latter method properly orders the relative antioxidant abilities of **4** and **5**, as measured by computed BDEs and ionization potentials. This encourages application of this method for the evaluation of other possible candidates for use as antioxidants.

Experimental Section

Melting points are uncorrected. IR spectra were obtained with a Beckman Acculab 8 spectrometer and calibrated against the 1601 cm^{-1} absorption of polystyrene. ^1H- and ^{13}C-NMR spectra were recorded of samples dissolved in $CDCl_3$ using a GE QE 300 spectrometer unless otherwise noted. GC-MS data were collected on a Finnigan MAT ITD 700 mass spectrometer equipped with a 15-m BP-5 capillary column, and HRMS data were obtained on a VG ZAB-E (Fisons) high-resolution mass spectrometer using the EI mode of ionization at 70 eV. Cyclic voltammetric measurements were measured with an EG & G Princeton Applied Research 173 potentiostat, 175 wave-form generator, and a Houston Instrument 2000 X-Y recorder. Unless stated otherwise, concentration of reaction mixtures was effected by rotary evaporation. Combustion analysis was performed by Galbraith Laboratories.

Ethyl 2,3-Dihydro-5-hydroxy-4,6,7-trimethyl-2-oxo-3-benzofurancarboxylate (7).[18] 2,3,5-Trimethyl-1,4-benzoquinone (**6**)[23] was allowed to react with diethyl sodiomalonate under the conditions described previously.[18] Following workup by removal of volatiles from the reaction mixture and *without* the steam distillation used previously,[18] crude **7** (93% yield) was isolated as a brown solid. Spectral data: ^1H-NMR (90 MHz) δ 1.30 (t, 3 H, J = 7.5 Hz), 2.20 (br s, 9 H), 4.29 (q, 2 H, J = 7.5 Hz), 4.63 (s, 1 H), 5.7 (br s, 1 H).

2,3-Dihydro-5-hydroxy-4,6,7-trimethyl-2(3*H*)-benzofuranone (10). Decarbethoxylation was achieved using the protocol of Krapcho et al.[19] A magnetically stirred solution of **7** (2.4 g, 9.2 mmol), water (302 mg, 16.8 mmol), and DMSO (7 mL), contained in a 25-mL round-bottom flask fitted with a reflux condenser, was heated at 110–120 °C for 1 h. The reaction mixture was brought to ambient temperature and diluted with water (20 mL) and diethyl ether (20 mL). The phases were separated, the aqueous layer was extracted with diethyl ether (2 × 20 mL), and the combined organic solutions were washed with brine (20 mL) and dried (Na_2SO_4). Concentration afforded 1.75 g (99% yield) of **10** as an off-white solid, mp 184–186 °C (lit.[22] mp 199 °C, lit.[18] mp 197–198 °C). Spectral data: ^1H-NMR (CD_3COCD_3) δ 2.13 (6 H), 2.16 (s, 3 H), 3.63 (s, 2 H), 7.05 (1 H); ^{13}C-NMR (CD_3CO-CD_3) δ 10.19, 10.33, 11.16, 31.29, 115.48, 117.53, 119.02, 122.26, 145.44, 147.96, 173.10; HRMS m/z calcd 192.078 64, found 192.078 31.

3,5,6-Trimethyl-1,4-hydroquinone Diallyl Ether (8).[24] The procedure used was one developed by Kornblum et al.[25] 2,3,6-Trimethyl-1,4-hydroquinone (Aldrich Chemical Co., 50 g, 0.33 mol) was dissolved in 210 mL of methanol contained in a 3-L round-bottom flask. The solution was degassed by sparging with argon, after which a solution of potassium hydroxide (40.5 g, 0.72 mol) in 65 mL of 85% aqueous methanol was added. The resulting mixture was concentrated, and the residue was dried for 24 h in vacuo (60 °C (1 mmHg)). The resulting dipotassium salt was dissolved in 1.6 L of anhydrous DMSO in a 3-L round-bottom flask, and allyl bromide (87.5 g, 0.72 mol) was added to this solution in a dropwise fashion over a period of 3 h. After being

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stirred at rt for 16 h, the reaction mixture was quenched with 300 mL of ice–water, and the solution that resulted was extracted with diethyl ether (5 × 175 mL). The combined extracts were washed with brine and dried (Na_2SO_4). Concentration and flash column chromatography over silica gel (benzene–Skellysolve B, 60:40, R_f = 0.41) afforded 8 (63% yield) as a colorless liquid. Spectral data: IR (neat) 3024, 1665, 1627, 1020, 950 cm^{-1}; ^1H-NMR (500 MHz) spectral data were within experimental error of those reported, with the exception that the multiplet for the internal vinyl hydrogen atoms ranged from δ 6.02 to 6.14 rather than the reported[24] 4.28–5.80 ppm; ^{13}C-NMR δ 12.00, 12.94, 16.51, 69.34, 73.47, 111.77, 116.61, 116.81, 124.09, 127.81, 130.74, 133.92, 134.25, 149.58, 152.53; GC–MS m/z 232 (M^+), 191, 41 (base peak).

2-Allyl-3,5,6-trimethyl-1,4-hydroquinone.[24] The reaction was conducted by modifying the procedure of Hammond et al.[26] A dry 1-L three-necked flask was charged with 226 mL of a 1.0 M solution of BCl_3 (0.23 mol) in dichloromethane and cooled to −60 to −70 °C under an atmosphere of dry nitrogen. A solution of the 2,3,6-trimethyl-1,4-hydroquinone diallyl ether (8, 47.7 g, 0.21 mol) in dichloromethane (375 mL) was added dropwise over a period of 0.5 h. The resulting solution became wine-red and was allowed to warm from −70 to 0 °C over a 4-h period. It was then cannulated into a beaker containing 1 L of ice–water, and the pale yellow precipitate that formed was collected by vacuum filtration. The liquid layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 100 mL). Concentration of the pooled extracts afforded 6 g of solids, which were combined with the filter cake and dried in vacuo (85 °C (0.3–0.1 mmHg)) to yield 2-allyl-3,5,6-trimethyl-1,4-hydroquinone (87% yield) as an off-white amorphous solid. It was used in the next step without further purification. Spectral data: ^1H-NMR δ 2.18 (s, 9 H), 3.43 (d, 2 H, J = 7.4 Hz) 4.45 (br s, 1 H) 4.55 (br s,) 5.04 (d, 1 H, J = 16.7 Hz), 5.09 (d, 1 H, J = 11.1 Hz), 5.86–6.20 (m, 1 H); ^{13}C-NMR (CD_3COCD_3) δ 12.03, 12.44, 31.38, 114.03, 121.71, 121.75, 122.35, 123.56, 137.44, 146.42, 146.52; GC–MS m/z 192 (M^+, base peak).

2-Allyl-1,4-diacetoxy-3,5,6-trimethylbenzene. A solution of 2-allyl-3,5,6-trimethyl-1,4-hydroquinone (34 g, 0.21 mol), acetic anhydride (134 mL), pyridine (135 mL), and Skellysolve B (70 mL) was stirred for 8 h at ambient temperature under a dry nitrogen atmosphere. The reaction mixture was quenched by addition of cold water (500 mL) and diethyl ether (800 mL). The aqueous layer was separated and extracted with diethyl ether (2 × 300 mL). The pooled organic layers were washed sequentially with 10% HCl (3 × 50 mL), saturated sodium bicarbonate solution (3 × 50 mL), water (50 mL), and saturated NaCl solution (50 mL). Drying (Na_2SO_4) and concentration of the organic solution afforded 2-allyl-1,4-diacetoxy-3,5,6-trimethylbenzene as a yellow oil (82% yield) that solidified on standing. Spectral data: ^1H-NMR δ 2.04 and 2.06 (s, 9 H), 2.32 and 2.34 (s, 6 H), 3.28 (br s, 2 H), 4.94 (d, 1 H, J = 18 Hz), 5.0 (d, 1 H, J = 11 Hz), 5.7–5.9 (m, 1 H); ^{13}C-NMR δ 12.47, 13.07, 20.29, 20.42, 31.78, 115.4, 127.36, 127.53, 127.92, 128.47, 134.97, 145.72, 145.97, 168.70, 168.90; GC–MS m/z 276 (M^+), 43 (base).

2′,5′-Diacetoxy-3′,4′,6′-trimethylphenylacetaldehyde. Ozonolysis of 2-allyl-1,4-diacetoxy-3,5,6-trimethylbenzene was conducted according to the method of Pappas et al.,[27] using Sudan III as an indicator. A 40-g sample of the substrate was dissolved in 1 L of methanol and 50 mL of dichloromethane. Sudan III (5–10 mg) was added, the solution was cooled to −60 °C, and ozone was passed through it at a rate such that the pink color of the solution was discharged within 2 h. The reaction mixture was then flushed with argon (15 min), and dimethyl sulfide (15 mL) was added. The resulting solution was stirred for 8 h and allowed to reach ambient temperature. Concentration of this solution afforded 2′,5′-diacetoxy-3′,4′,6′-trimethylphenylacetaldehyde as a pale pink microcrystalline solid, mp 118–122 °C (98% yield). Spectral data: IR ($CHCl_3$) 1740, 1710 cm^{-1}; ^1H-NMR δ 2.06 and 2.10 (s, 9 H), 2.31 and 2.36 (s, 6 H), 3.57 (br s, 2 H), 9.57 (t, 1 H, J = 1.8 Hz); ^{13}C-NMR δ 12.98, 20.20, 42.51, 121.84, 127.75, 127.81, 129.56, 145.80, 168.64, 168.87, 198.26.

2′,5′-Diacetoxy-3′,4′,6′-trimethylphenylacetic Acid (9). A solution of 2′,5′-diacetoxy-3′,4′,6′-trimethylphenylacetaldehyde (38.3 g, 0.14 mol) was dissolved in 990 mL of acetone (freshly distilled from $KMnO_4$). Jones' reagent[28] was then added dropwise until an orange-brown color persisted; the temperature of the solution was held at or below room temperature throughout this addition. The resulting mixture was stirred for 20 min and diluted with saturated NaCl solution, and the crude product was isolated by repeated extractions with ether. The combined extracts were dried (Na_2SO_4) and concentrated to afford 35.5 g (87% yield) of 9 as a white solid, mp > 180 °C dec. Spectral data: IR (Nujol) 3230–2530, 1780, 1730 cm^{-1}; ^1H-NMR δ 2.04, 2.08 and 2.12 (3s, 9 H), 2.34 and 2.36 (2s, 6H), 3.58 (br s, 2 H), 8.00 (br s, 1.3 H); ^{13}C-NMR δ 13.08, 13.24, 20.37, 33.14, 123.58, 127.91, 128.08, 129.60, 145.93, 146.06, 168.69, 169.89, 175.27.

2,3-Dihydro-5-hydroxy-4,6,7-trimethyl-2(3*H*)-benzofuranone (10). To suppress formation of quinone as a byproduct, oxygen was rigorously excluded from the reaction vessel. A solution of potassium carbonate (0.72 g, 5.2 mmol) in MeOH/H_2O (28:16 mL) was added to a solution of 9 (0.59 mg, 2 mmol) in MeOH (60 mL). Each solution had been previously degassed by sparging with argon for 25 min. The resulting solution, under argon, was refluxed for 2 h and then stirred overnight at room temperature. Concentrated HCl was added to bring the pH to 3 (pHydrion paper), the resulting solution was concentrated to 5–10 mL and diluted with 5 mL of H_2O and 20 mL of diethyl ether, and the layers were separated. The aqueous layer was washed with diethyl ether (4 × 10 mL), and the ethereal extracts were pooled, washed with saturated NaCl solution (15 mL), and dried (Na_2SO_4). Concentration afforded lactone 10 as a yellow solid (98% crude yield).

5-(*tert*-Butyldimethylsiloxy)-4,6,7-trimethyl-2(3*H*)-benzofuranone. Silylation of 10 was achieved using *tert*-butyldimethylsilyl chloride and imidazole, according to the method of Corey and Venkateswarlu.[29] Yields of crude product were quantitative. The product was purified by flash column chromatography over silica gel using a solvent system of Skellysolve B and ethyl acetate (90/10, R_f = 0.37). The colorless solid that resulted had mp 105–107 °C. Spectral data: ^1H-NMR δ 0.15 (s, 6 H), 1.05 (s, 9 H), 2.04, 2.06 and 2.08 (3s, 9 H), 3.55 (s, 2 H); ^{13}C-NMR δ −3.17, 12.67, 14.06, 14.51, 18.68, 26.09, 33.24, 117.84, 119.71, 122.20, 127.95, 147.54, 148.08, 174.56; HRMS m/z calcd 306.165 12, found 306.165 95.

5-(*tert*-Butyldimethylsiloxy)-2-methylene-4,6,7-trimethyl-(3*H*)-benzofuran (11). A three-necked 100-mL round-bottom flask was fitted with a magnetic stirring bar, addition funnel, and septa. It was flame-dried and cooled under a steady stream of argon. 5-(*tert*-Butyldimethylsiloxy)-4,6,7-trimethyl-2(3*H*)-benzofuranone (3 g, 9.8 mmol) was placed in the flask, and the septa were secured with wire. The lactone was dissolved in dry THF (30 mL) and pyridine (72 μL, 10 mol %), the solution was cooled to 0 °C, a stock solution of Tebbe's reagent[17,30] in toluene (0.75 M, 15.7 mL, 1.2 equiv) was cannulated into the addition funnel using argon and then added to the reaction vessel over a period of 5–10 min. The reaction mixture was stirred for 30 min at 0 °C and a further 1.5 h at ambient temperature. It was then cooled to 0 °C and slowly quenched with 9.4 mL of 10% aqueous NaOH. The mixture was taken up in 500 mL of dichloromethane and filtered through a pad of diatomaceous earth, and the filtrate was dried (Na_2SO_4) and concentrated. Concentration afforded a residue that was dissolved in hexane and passed through a short column (1.5-in. long, 55-mm i.d.) of basic aluminum oxide which had been saturated with triethylamine; deactivation of the stationary phase with the amine was essential to prevent double-bond migration in the product. The yellow solution that was collected was concentrated to afford 11 as a yellow oil (50% yield), which was immediately cyclopropanated to minimize losses due to isomerization of the double bond. Spectral data: ^1H-NMR (90 MHz) δ 0.70 (s, 6 H), 0.98 (s,

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9 H), 2.07 (s, 9 H), 3.73 (br s, 2 H), 4.15 (q, 1 H, J = 2 Hz), 4.62 (q, 1 H, J = 2 Hz); GC–MS m/z 304 (M^+), 247 (base).

Spiro[2,3-dihydro-5-(*tert*-butyldimethylsiloxy)-4,6,7-trimethylbenzofuran-2,1′-cyclopropane]. Cyclopropanation of 11 was conducted according to the method of Furukawa et al.[16] A 1.29-g sample of 11 (4.24 mmol) was dissolved in 6 mL of dry diethyl ether. To this solution, under argon, was added a 1 M solution of diethylzinc in hexanes (3.3 mL, 3.30 mmol) and diiodomethane (0.42 mL, 5.3 mmol). The reaction mixture was refluxed under argon for 4 h, held at ambient temperature for 8 h, and then quenched with water (10 mL). Following extraction of the mixture with diethyl ether (4 × 15 mL), the combined organic solutions were washed with brine and dried (Na_2SO_4). Filtration and concentration afforded the desired product (93% yield) as an off-white solid. Spectral data: ^{1}H-NMR (90 MHz) δ 0.10 (s, 6 H), 0.65 (br s, 2 H), 1.13 (br s, 2 H), 2.08 (br s, 9 H), 3.27 (br s, 2 H); GC–MS m/z 318 (M^+), 261; HRMS m/z calcd 318.201 51, found 318.201 18.

Spiro[2,3-dihydro-5-hydroxy-4,6,7-trimethylbenzofuran-2,1′-cyclopropane] (5). A 196-mg sample of spiro[2,3-dihydro-5-(*tert*-butyldimethylsiloxy)-4,6,7-trimethylbenzofuran-2,1′-cyclopropane] (0.62 mol) was stirred with tetrabutylammonium fluoride (489 mg, 1.55 mmol) in 11 mL of dry THF. After 1.5 h the solution was diluted with water (20 mL) and washed with diethyl ether (5 × 10 mL). The pooled extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to afford 115 mg (92% yield) of crude phenol 4. Sublimation (95 °C (0.25 mmHg)) provided 4 as a white microcrystalline solid, mp 179–182 °C. Spectral data: ^{1}H-NMR (DMSO-d_6) δ 0.70 (m, 2 H), 1.2 (m, 2 H), 1.93 (s, 3 H), 2.03 (s, 6 H), 3.15 (s, 2 H), 7.50 (s, 1 H); ^{13}C-NMR (DMSO-d_6) δ 12.07, 12.43, 13.30, 35.94, 66.25, 114.30, 118.85, 122.28, 122.77, 146.22, 150.72; GC–MS m/z 204 (M^+), 189 (base), 176; HRMS m/z calcd 204.115 03, found 204.114 68. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.26; H, 8.00.

Acknowledgment. We thank Dr. David Martella (Exxon) for the determination of k_1 of 5, Dr. Vincent Lynch for the X-ray crystal structures, and Dr. Yate-Ching Yuan for assistance with the theoretical calculations. The financial support of this work by Alcon Laboratories is gratefully acknowledged.

Supplementary Material Available: ^{1}H-NMR spectra of 2-allyl-1,4-diacetoxy-3,5,6-trimethylbenzene, 2′,5′-diacetoxy-3′,4′,6′-trimethylphenylacetaldehyde, 2′,5′-diacetoxy-3′,4′,6′-trimethylphenylactic acid (9), 5-(*tert*-butyldimethylsiloxy)-2-methylene-4,6,7-trimethyl-(3*H*)-benzofuranone, 5-(*tert*-butyldimethylsiloxy)-2-methylene-4,6,7-trimethyl-(3*H*)-benzofuran (11), and spiro[2,3-dihydro-5-(*tert*-butyldimethylsiloxy)-4,6,7-trimethylbenzofuran-2,1′-cyclopropane] (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Additions and Corrections

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Dale L. Boger,* Royce F. Menezes, and Qun Dang. Synthesis of Desacetamidopyrimidoblamic Acid and Deglyco Desacetamidobleomycin A_2.

Page 4336. Text was inadvertently published in the Acknowledgment section. The last paragraph and Acknowledgment should read as follows.

A preliminary study of the ability of the Fe(II) complex of 4 to cleave duplex DNA was conducted through examination of single-strand and double-strand cleavage of supercoiled ϕX174 RFI DNA (Form I) to produce relaxed (Form II) and linear (Form III) DNA, respectively. Like Fe(II)-bleomycin A_2[17] and deglycobleomycin A_2[17], Fe(II)-4 produced both single- and double-strand cleavage of ϕX174 RFI DNA, Figure 2. The direct comparison of the efficiency of DNA cleavage by Fe(II)-4 and Fe(II)-deglycobleomycin A_2 permits the assessment of the relative importance and functional role of the pyrimidoblamic acid C2 acetamido side chain. Although the side chain has been shown not to be intimately involved in the metal chelation, it has been suggested to contribute to the efficiency of DNA cleavage by constituting one side or component of the oxygen binding pocket thereby sterically shielding or protecting the activated and reactive iron-oxo intermediate.[1] Consistent with this latter suggestion, Fe(II)-deglycobleomycin A_2 proved to be 3–5× more effective than Fe(II)-4 in its efficiency for producing the cleavage of supercoiled ϕX174 RFI DNA, Figure 3 [relative efficiency: bleomycin A_2 (1), deglycobleomycin A_2 (0.5–0.2), 4 (0.2–0.05)]. Under the conditions of the assay, both Fe(II)-deglycobleomycin A_2 and Fe(II)-4 produced little or no cleavage at 0.2 μM, significant cleavage at 1 μM, and complete cleavage at 5 μM. Both agents proved to be slightly less efficient that Fe(II)-bleomycin A_2 which produced significant cleavage of the supercoiled DNA at concentrations as low as 0.2 μM with complete cleavage of the DNA at 1 μM. Consistent in each of multiple assays, Fe(II)-deglycobleomycin A_2 proved at least as effective in producing linear DNA resulting from double-stranded DNA cleavage as Fe(II)-bleomycin A_2 itself which in turn generally proved more effective than Fe(II)-4. Detailed studies of the DNA cleavage properties of Fe(II)-4 including additional comparison of its duplex DNA cleavage efficiency and selectivity with that of bleomycin A_2, deglyco bleomycin A_2, and structurally related analogs are in progress and will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA42056). We wish to thank Dr. W. Yang for conducting the DNA cleavage studies of Fe(II)-4 and Professor S. M. Hecht for copies of the ^{1}H NMR spectra of 17 and desacetamidopyrimidoblamic acid (3).