Antioxidant Activity of Phenols Related to Vitamin E. Are There Chain-Breaking Antioxidants Better Than α-Tocopherol?[1]

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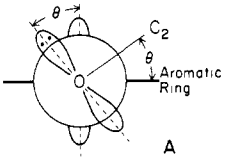
α-Tocopherol (**1**) is not only the most important constitutent of Vitamin E, but as we have previously reported,[2] it is also one of the two best chain-breaking, phenolic antioxidants known. That is, **1** and the structurally related model compound **2** react more rapidly with peroxyl radicals (reaction 1) than any of the numerous

$$ROO\cdot + ArOH \rightarrow ROOH + ArO\cdot \quad (1)$$

other phenols investigated. Comparison of the k_1 values for **1** (and **2**) with those found for structurally related phenols that lacked the fused 6-membered heterocyclic ring showed that this ring was largely responsible for the high reactivity of α-tocopherol. This ring exerts a stereoelectronic effect by constraining the ring oxygen in such a manner that its p-type lone pair is rather well oriented to stabilize the developing phenoxyl radical.[2] The superior antioxidant behavior of **1** is further supported by our recent finding that it accounts for most, if not all, of the antioxidant capacity of the lipid fractions of human blood plasma and red blood cells.[3,4]

However, the question still arises: are chain-breaking antioxidant structural features fully optimized in α-tocopherol? More specifically, is the stereoelectronic effect maximized in **1** and **2**, or are there other structures that express the effect more fully? We have approached this question by measuring the k_1 values of selected compounds by the inhibited-autoxidation method[2] using styrene as the oxidizable substrate and a very much improved apparatus. Some of the compounds[5] we have examined are given in Table I together with their k_1 values at 30 °C. The effect of structural changes on k_1 values can be conveniently divided into four categories.

1. Chromans with Alkyl Groups or Hydrogen at Position 2 (1–3). The differences in reactivity of **1**, **2**, and **3** are small but certainly real. We tentatively suggest that these differences are due in part, at least, to changes in the conformation of the heterocyclic ring. That is, an X-ray crystallographic analysis of **2** has shown[2] that the dihedral angle between the aromatic ring and the O–C_2 bond is ca. 16°. This implies that the 1-oxygen's 2p-type lone pair has a dihedral angle, θ, of 16° with respect to the axis of the p orbital at the adjacent aromatic carbon, A. Better



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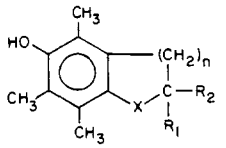
stabilization of the phenoxyl radical, and hence a larger k_1, should be achieved by decreasing θ, optimum stabilization occurring for θ = 0°. In the crystal, the heterocyclic ring of **2**, adopts a half-chair conformation,[2] the extent of ring puckering being to some extent limited by a 1,3 steric interaction between the pseudoaxial 4-H and 2-CH_3. Replacing both 2-CH_3 groups in **2** by H will allow ring puckering to increase, which will make θ increase. Hence, k_1 will decrease, as is observed. The bulky phytyl group in **1** may also increase puckering.

Table I



compd	n	R_1	R_2	X	$10^{-5}k_1$, M^{-1} s^{-1} [a]	k_1/k_1^1
1	2	CH_3	$C_{16}H_{33}$	O	32.4 ± 1.5	(1.00)
2	2	CH_3	CH_3	O	37.7 ± 1.9	1.16
3	2	H	H	O	26.7 ± 1.3	0.82
4	2	CH_3	C(O)OH	O	11.0 ± 0.7	0.34
5	2	CH_3	$C(O)OCH_3$	O	18.3 ± 0.9	0.56
6	2	CH_3	$CH_2C(O)OH$	O	18.7 ± 0.9	0.58
7	2	H	H	NH		
8	2	H	H	$NC(O)CH_3$	1.2 ± 0.1	0.04
9	2	H	H	NCH_2CH_3	19.7 ± 1.0	0.61
10	1	H	CH_3	O	53.9 ± 2.7	1.66

[a] The k_1 values obtained in 14 separate runs with **1** gave a standard deviation of 5%. Two or more runs were made with all the other phenols, the differences between the individual runs for each phenol being less (often considerably less) than 5%. Nevertheless, 5% error limits have been given for all the phenols.

2. Chromans with Oxygenated Substituents at Position 2 (4–6). It has been reported that **4** is superior to **1** as an antioxidant in a number of food preservation tests.[6-9] Since **4** is less reactive than **1** toward ROO· in homogeneous nonpolar solvents, its effectiveness in food preservation must have some other origin. Similarly, **5** and **6** were less effective food preservatives than **4**,[6] although both are more reactive toward ROO· radicals.

The decreased reactivity toward ROO· of **4**, **5**, and **6** relative to **1** we tentatively attribute to the electron-withdrawing carboxyl group, which by the inductive effect impairs the ability of the p-type lone pair on the ring oxygen to participate in the stabilization of the phenoxyl radical. Consistent with this explanation, **6**, which has an additional carbon attenuating the inductive effect, shows a reactivity intermediate between **1** and **4**. Since **5** is more reactive than **4** there would appear to be a specific deactivating effect due to a CO_2H group,[10] such as hydrogen bonding.[13]

3. Tetrahydroquinolines (7–9). We had expected that **9**[14] would be a better antioxidant than **1** because nitrogen, being less electronegative than oxygen, would be better able to stabilize the neighboring radical center by conjugative delocalization of its lone pair of electrons. However, an inspection of space-filling models indicates that there will be very severe steric interactions between an equatorial *N*-ethyl group and the 8-methyl group. As a consequence, the *N*-ethyl group must adopt the axial position.[16] The nitrogen's lone pair will therefore lie rather close to the plane of the aromatic ring and hence will be in a relatively unfavorable position to stabilize the incipient phenoxyl radical.

The amide **8**, which also exhibits severe steric interactions,[15] is a great deal less reactive than **9**, which can be attributed to the electron-withdrawing effect of the acetyl group.

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4. 2,3-Dihydrobenzofuran (10). Since 5-membered rings are generally more planar than 6-membered rings it seemed probable that θ would be decreased by reducing the heterocyclic ring to this size. In the one phenol of this class that we have been able to examine,[16] i.e., **10**, the reactivity toward peroxyl radicals is enhanced by a factor of 1.66 relative to **1** or 1.43 relative to **2**. This enhancement in k_1 is larger than the factor of 1.1, which can be calculated assuming a $\cos^2\theta$ dependence for orbital overlap with $\theta = 0°$ and 16° for **10** and **2**, respectively. This is a surprising result, which we are investigating further, but it remains to be seen whether an analogue of **10** having appropriate lipophilicity would show greater Vitamin E activity than α-tocopherol.

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Registry No. 1, 86646-82-4; **2**, 950-99-2; **3**, 21704-70-1; **4**, 56305-04-5; **5**, 86646-83-5; **6**, 86646-84-6; **7**, 50869-01-7; **8**, 50869-02-8; **9**, 86646-85-7; **10**, 86646-86-8.

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

Dramatic Salt Effects on the Basic and Nucleophilic Properties of Superoxide Radical Anion Generated from O_2 and Iron(I) "Electron-Reservoir Complexes"[1]

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The superoxide radical anion has attracted considerable attention recently because of its role in the degradation of red cells, membranes, granulocytes, and bacteria.[2] In particular its properties as a base, nucleophile, ligand, reducing agent, and its photon- and transition-metal-induced reduction and disproportionation have been studied.[3] In these investigations, chemists were compelled to use KO_2 in Me_2SO or in THF with stoichiometric 18-crown-6 because of the insolubility of superoxide salts; the only alternative was electrogeneration of $O_2^{-}\cdot$ in pyridine or DMF. Our approach has consisted of generating $O_2^{-}\cdot$ from dioxygen or air and neutral Fe^{I} "electron-reservoir complexes"[4,5] under mild conditions. A spectacular H atom abstraction observed in such systems is the result of rapid outer-sphere electron transfer to O_2 followed by deprotonation by $O_2^{-}\cdot$ in the cage (eq 1).[5]

$$\underset{\mathbf{1}}{CpFe^{I}(\eta^6\text{-}C_6Me_6)} \xrightarrow{O_2 \text{ or air}} \underset{\mathbf{2}}{CpFe^{II}(\eta^5\text{-}C_6Me_5CH_2)} \quad (1)$$

Table I. Salt Effect on the Reactivity of $O_2^{-}\cdot$ as a Base in the Reaction 1 $\xrightarrow[-80\ °C,\ THF]{O_2}$ 2 (1)[a]

M^+X^-[c]	2	1^+X^-
without	92[b]	8[b]
$n\text{-}Bu_4N^+PF_6^-$	85	15
$K^+PF_6^-$	45	55
$K^+PF_6^-$ + 18-6 (stoich)	83	17
$Na^+PF_6^-$	0	100
$Na^+BF_4^-$	30	70
Na^+F^-	65	35

[a] See also eq 4 and 6. Percent of 2 and 1^+X^- determined by weight (reactions are immediate). [b] At 20 °C, the crude yields are 2, 97%; $1^+PF_6^-$, 3%.[5a-c] [c] Concentrations of both 1 and the salt in THF (30 mL) are 0.033 mol L^{-1}. With other $CpFe^{I}$(arene) complexes (arene = toluene, mesitylene, pentamethylbenzene, ethylbenzene, fluorene), analogues of 2 are not formed in the presence of 1 equiv of $Na^+PF_6^-$ under identical conditions [90–100% yield of $(CpFe(arene))^+PF_6^-$].

We also know that in the absence of benzylic hydrogens, formation of a neutral peroxide occurs,[6] although the mechanism was unknown.

$$\underset{\mathbf{3}}{2CpFe^{I}(\eta^6\text{-}C_6H_6)} + O_2 \xrightarrow[-80\ °C]{\text{toluene}} \underset{\mathbf{4}}{[CpFe^{II}(\eta^5\text{-}C_6H_6O\text{-})]_2} \quad (2)$$

We now wish to report salt effects on the reactivity of $O_2^{-}\cdot$ generated in these systems from O_2 or air and Fe^{I} complexes.

The starting point for these findings was an attempt to generalize the benzylic C–H activation reaction of eq 1 to other arene Fe^{I} complexes[7] (arene = toluene, ethylbenzene, mesitylene, pentamethylbenzene, fluorene). The major problem was that $CpFe^{I}$(arene) complexes are unstable above −15 °C in THF or DME solution in which they are synthesized by Na/Hg reduction of their precursor 18-electron d^6 PF_6^- salts. Thus $^1/_2$ mol of O_2 was added at −80 °C to such forest-green solutions subsequent to synthesis at −20 °C (1 h) and filtration by canula. A yellow precipitate and a colorless solution were always obtained by this procedure whatever the arene ligand in the sandwich complex and in particular whether or not it bears benzylic hydrogen(s). $CpFe^{+}$(arene)PF_6^- can be extracted from the precipitate with CH_2Cl_2, leaving white insoluble Na_2O_2 characterized by the peroxide stretch at 805 cm^{-1} in the IR spectra (eq 3). On the

$$(CpFe^{II}(arene))^+PF_6^- \underset{\text{THF, } -20\ °C}{\overset{Na/Hg}{\longrightarrow}} CpFe^{I}(arene) + Na^+PF_6^- \quad (3)$$
$$\xrightarrow[-\,^1/_2 Na_2O_2]{^1/_2 O_2\ (-80\ °C)}$$

other hand, if $NaPF_6$ is eliminated from the THF solution[9] prior to the addition of O_2, no precipitate is formed; the stoichiometry in O_2 remains $^1/_2$ mol and the solution turns dark red if a benzylic hydrogen is present on the arene and orange otherwise. The

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