Transition-metal complexes have been used extensively to catalyze the transfer of carbene moieties from diazoalkanes to olefins.[1,14] It is often assumed that the metal center attacks the unique *carbon* of the diazoalkane, displacing N_2. The results reported here suggest that this view may be naive; the catalytically active species may be N bonded or polynuclear.

Complexes containing μ-alkylidene ligands are a small but growing class of compounds of considerable chemical[15] and theoretical[16] interest, and their reaction chemistry is still largely unexplored.[17] Pettit et al. have recently stressed the role of bridging alkylidenes in Fischer–Tropsch reductions of carbon monoxide to alkanes.[18]

Further chemistry of complexes of types **2** and **3** bearing on these points will be reported in the near future.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the Americal Chemical Society, and the National Science Foundation (Grant CHE-7907748) for support of this research. We thank Professor R. Hoffmann for a preprint describing calculations on bridging methylene complexes.

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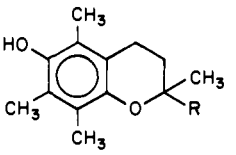
Received July 25, 1980

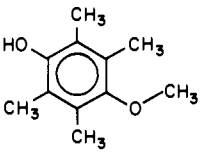
Antioxidant Activity of Vitamin E and Related Phenols. Importance of Stereoelectronic Factors[1]

Sir:

There is now a rather general agreement that α-tocopherol (**1**), the major component[2] of vitamin E, functions as an efficient inhibitor of lipid peroxidation in vivo,[3] but there is widespread confusion regarding its absolute antioxidant effectiveness in vitro. Comparisons of **1** with other natural and synthetic phenols have usually led to the conclusion that it has only a rather modest



1 R = $[CH_2CH_2CH_2CH(CH_3)]_3CH_3$



2

3 R = CH_3

antioxidant activity in vitro.[4] The apparent "discrepancy" between the high in vivo vitamin E activity of **1** and its apparently low in vitro antioxidant activity has generally been accepted uncritically. This is surprising because **1** has just those structural features in its phenolic moiety which would lead one to predict that it would be a highly efficient chain-breaking (peroxyl radical trapping) antioxidant.[5,6] That is, inhibition by phenols involves reactions 1 and 2,[5] and the magnitude of the rate constant for the rate

$$ROO\cdot + ArOH \xrightarrow{k_{inh}} ROOH + ArO\cdot \quad (1)$$

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

controlling step, k_{inh}, has been shown, in a comprehensive survey of the effect of ring substituents on the rate of reaction (1),[6] to be increased by a 4-methoxy group and by methyl groups in the 2, 3, 5, and 6 positions.[7] Furthermore, chain transfer via ArO· (which reduces the effectiveness of ArOH) is retarded when the phenoxyl oxygen is sterically protected by alkyl groups in the 2 and 6 position.[5b,5c] Chain transfer is also retarded by the electron-donating 4-methoxy group.[5b]

In an attempt to reconcile the structure of **1** with its purported low in vitro antioxidant activity, we have measured k_{inh} for **1** in the well-proven autoxidation system of styrene under 760 torr of O_2, thermally initiated with azobis(isobutyronitrile).[6,8] The standard induction period method[9] showed that **1**, like the majority of phenols,[5,6,8a,10] reacts with two peroxyls, i.e., the stoichiometric factor (n) is 2.0, as would be expected for reactions 1 and 2. For **1** at 30 °C, $k_{inh} = (23._5 \pm 5._0) \times 10^5\ M^{-1}\ s^{-1}$, which indicates that it is an extremely efficient phenolic chain-breaking antioxidant,[5,6,8a,11] just as we anticipated. Deuteration of the phenolic hydrogen in the usual way[6,8a] reduces the antioxidant activity of α-tocopherol, $k_{inh}^H/k_{inh}^D = 4.0 \pm 0.5$, showing that H-atom abstraction (reaction 1) is rate controlling, as with other phenols.

We expected that 4-methoxy-2,3,5,6-tetramethylphenol, **2**, would be equally reactive. This phenol has $n \sim 2.0$ and $k_{inh}^H/k_{inh}^D = 10.6 \pm 3.7$, but to our great surprise it has $k_{inh} = (2._1 \pm 0._2) \times 10^5\ M^{-1}\ s^{-1}$ at 30 °C. To discover whether the "vital force" (magic) of **1** resides in the phytyl side chain (R in **1**) or in the

(1) Issued as N.R.C.C. 18858.

(2) Generally ~85%; the other three components (β-, γ-, and δ-tocopherol) are close structural relatives to **1**.

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(7) Values of k_{inh} for ring substituted ArOH can be correlated via the Hammett equation using Brown's σ^+ substituent constants.[6] Phenols having different degrees of steric protection of the OH group give different correlation lines, but all have a large negative slope,[6] i.e., ρ is negative.

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(11) Literature values[12] of k_{inh} for **1** range from 2×10^5 to $5 \times 10^8\ M^{-1}\ s^{-1}$.

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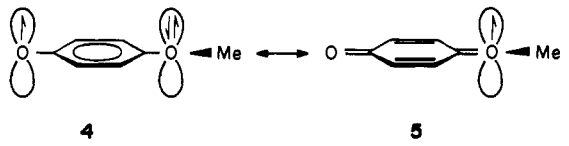
Table I. Relevant X-ray Diffraction Data on Some 4-Alkoxyphenols

structural parameter	angles, deg: dihedral Ar-O-C	angles, deg: interbond Ar-O-C	bond lengths, Å: Ar-OR	bond lengths, Å: ArO-R
2	88.6	113.5	1.408	1.443
3(A)[a]	14.5	117.0	1.389	1.463
3(B)[a]	18.0	116.7	1.392	1.448
8	8.3	117.6	1.377	1.397
9	25.3	117.2	1.397	1.420

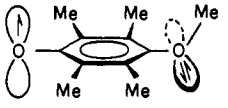
[a] There are two symmetry-unrelated molecules in the unit cell for 3.

chroman ring system, we synthesized **3** for which we find $n \sim 2.0$, $k_{inh}^{H}/k_{inh}^{D} = 5.5$ and $k_{inh} = (21.4 \pm 8.1) \times 10^5$ M^{-1} s^{-1} at 30 °C. Therefore, in vitro at least,[13] the magic of **1**'s antioxidant powers resides in some difference in the properties of the fused chroman ring system of **1** and **3** and those of the simple aromatic ring of **2**.

The initial clue to the origin of this difference came when we found that k_{inh} for **2** was only 1.5 times larger than that for pentamethylphenol. For other pairs of 4-methoxyphenols and 4-methylphenols, both unsubstituted elsewhere and substituted with alkyl groups in the 2 and/or 6 positions, the former compounds are ~5 times as reactive as the latter.[5,6,8a] The methoxy group in **2** is not, therefore, exerting a "normal" accelerating effect in reaction 1. The normal enhancement of k_{inh} by a 4-methoxy group is due to stabilization of the phenoxyl formed in reaction 1 by delocalization of the unpaired electron to the p-type orbital of the methoxyl oxygen, **4** ↔ **5**.[15] Such an interaction would be



4 **5**



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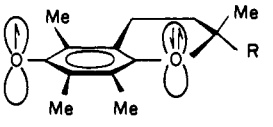

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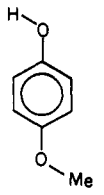
prohibited if the methoxyl in **2** were twisted out of the plane of the aromatic ring, i.e., **6**. However, for **1** and **3**, the fused ring structure should hold the p-type lone pair of the chroman oxygen more or less perpendicular to the aromatic plane, thereby stabilizing the product phenoxyl, **7**. The magnitude of the stabilization of **7** relative to **6** can be estimated to be ~3 kcal/mol.[17]

This stereoelectronic explanation for the high in vitro reactivity of **1** and **3** relative to **2** was tested by X-ray analysis of **2** and **3**, and 4-methoxyphenol (**8**) and 2,6-di-*tert*-butyl-4-methoxyphenol (**9**), as two examples of compounds not having alkyl substituents in positions 3 and 5. Some of the more significant structural parameters are listed in Table I. It can be seen that the Ar–O–C dihedral angle is ~90° for **2** (cf. **6**). However, it is only ~16° for **3** (cf. **7**), which is of similar magnitude to the angles found for **8** and **9**.



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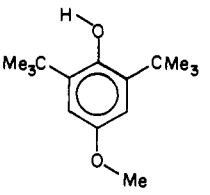

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In summary, the chroman ring system maintains a near-optimal orientation of the ethereal oxygen p-type lone pair with respect to the aromatic ring which, in combination with alkyl substitution at the other four ring positions, explains the superior chain-breaking antioxidant properties of α-tocopherol and **3**. Full details of this and other kinetic work and of the X-ray analyses will be published elsewhere.

Acknowledgment. We thank Dr. J. A. Howard and Dr. J. N. Thompson for helpful discussions.

Supplementary Material Available: Crystal data, data collection information, atomic positional and thermal parameters for **2**, **3**, **8**, **9** (11 pages). Ordering information is given on any current masthead page.

(13) In vivo, however, **3** does not show vitamin E activity[14] and so the phytyl is vital.

(14) Skinner, W. A.; Parkhurst, R. M.; Scholler, J.; Alaupovic, P.; Crider, Q. E.; Schwarz, K. *J. Med. Chem.* **1967**, *10*, 657. Skinner, W. A.; Parkhurst, R. M. *Lipids* **1970**, *5*, 184.

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

(17) Based on the fact that the k_{inh} values for **1** and **3** are about 10 times the value for **2** and the relationship between k_{inh} and phenolic O–H bond strengths given in ref 16.

(18) N.R.C.C. Research Associate 1978–1980.

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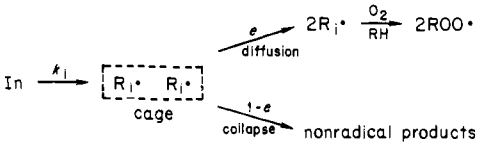
Received June 4, 1980

Autoxidation of a Model Membrane. A Comparison of the Autoxidation of Egg Lecithin Phosphatidylcholine in Water and in Chlorobenzene[1]

Sir:

A large body of quantitative kinetic information regarding the autoxidation of many organic substrates in homogeneous solution is now available, and the overall process is very well understood.[2] In contrast, the autoxidation of biological membranes, though known to occur readily and to be associated with many important pathological events,[3] is totaly lacking in quantitative kinetic data. In this communication we report some results from a kinetic study of the thermally initiated autoxidation of egg lecithin phosphatidylcholine at 30 °C in homogeneous solution in chlorobenzene and as bilayer dispersions (vesicles or model membranes) in 0.1 M aqueous NaCl. Our results provide answers to three simple, but extremely important, questions concerning the autoxidation of lecithin bilayers, answers which we hope will prove relevant to the autoxidation of biomembranes.

(1) Is There a Large Cage-Effect in a Lecithin Bilayer? In kinetically controlled autoxidations an initiator, In, decomposes to produce two radicals.[2] These may react together within the



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