Products and Stoichiometry of Reaction of Vitamin E with Alkylperoxy Radicals

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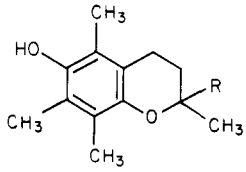
Oxidation of vitamin E (α-tocopherol, E) at 50 °C in acetonitrile and hexane by alkylperoxy radicals gives up to 50% yield of the 4-(alkylperoxy)cyclohexadienone derived from combination of $RO_2\cdot$ and E radicals; this product rapidly hydrolyzes to tocopherylquinone. E consumes two $RO_2\cdot$ radicals, and kinetic studies indicate that the rate constant for $RO_2\cdot + E \rightarrow RO_2H + E\cdot$ is greater than 2×10^5 M^{-1} s^{-1}.

Introduction

Vitamin E (**1**, E) is the important natural phenolic an-



1 (*d*-α-tocopherol, E), R = $C_{16}H_{33}$

tioxidant found in animal cell membranes and is believed to play an essential role in minimizing cellular oxidation by peroxy free radicals.[1-3] E also is a partly hindered phenol and would be expected to react like other hindered phenols according to reactions 1–4 (ArOH = E). Further reactions of dimers with $RO_2\cdot$ are suppressed with excess ArOH.

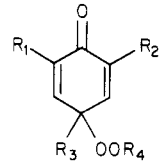
$$RO_2\cdot + ArOH \rightarrow RO_2H + ArO\cdot \quad (1)$$

$$RO_2\cdot + ArO\cdot \rightarrow RO_2\text{–}ArO \quad (2)$$

$$RO_2\cdot + ArO\cdot \rightarrow RO_2H + \text{quinomethide (QM)} \quad (3)$$

$$2ArO\cdot \xrightarrow{k_8} \text{dimers} \quad (4)$$

If the phenol has bulky alkyl groups at positions 2 and 6, reaction 4 is slow and reactions 2 and 3 dominate.[4-7] With 2,6-di-*tert*-butyl-4-methylphenol (BHT), and other *tert*-butyl-hindered phenols, the principal product is the 4-(alkylperoxy)-2,5-cyclohexadienone **2** from reaction 2.[4-8] Ortho coupling or disproportionation sometimes is observed in reactions 2 and 3 with *o*-methyl-substituted phenols.[8]



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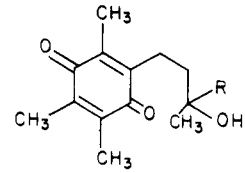
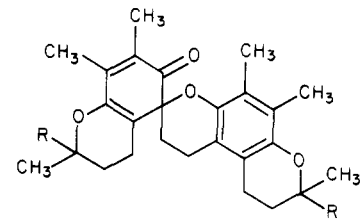
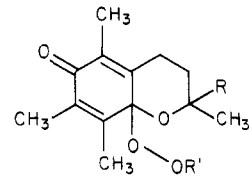
The products of $RO_2\cdot$ reactions with E at high concentrations in homogeneous solution have been reported previously to be α-tocopherylquinone (**3**) and spiro dimer **4**.[9-11] In a preliminary report, we indicated that, in solution at lower concentrations, E forms peroxy ketal **5** from $RO_2\cdot$ and E· via reaction 2.[12] Inglett and Matill[13] suggested



3 (α-tocopherylquinone), R = $C_{16}H_{33}$



4 (α-tocopheryl spiro dimer), R = $C_{16}H_{33}$



5a, R = $C_{16}H_{33}$; R′ = $C(CN)(CH_3)_2$
b, R = $C_{16}H_{33}$; R′ = $C(CO_2\text{-}n\text{-}Bu)(CH_3)_2$

that an analogous coupling product may be formed from the coupling of benzoyloxy radical with the chromanoxy radical derived from the E model 2,2,5,7,8-pentamethyl-6-hydroxychroman.

The value of the H-atom transfer constant from E to RO_2 (k_1 in reaction 1) is a measure of the effectiveness of E as a lipid antioxidant in biological cell walls where roughly one E is present for every 10 000 lipid molecules.[3] Recent estimates of k_1 at 25–30 °C range from 1.5×10^5 M^{-1} s^{-1} by chemiluminescent measurements on reactions of E with 1-phenethylperoxy radical[14] to 2.3×10^6 M^{-1} s^{-1} for reaction of E with polystyrylperoxy radical.[15] A very

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much higher value of 5×10^8 M^{-1} s^{-1} reported for reaction of E with (trichloromethyl)peroxy radical[16] probably reflects a different process, electron transfer, and is not likely to be applicable to oxidation in biological systems except under special circumstances such as intoxication by carbon tetrachloride.

Discrepant values of the radical scavenging efficiency (n) of E also have been reported for scavenging of $RO_2\cdot$ by E, determined by different methods. Burton and Ingold[15] measured oxygen uptake by solutions of radical initiators and E in chlorobenzene–styrene and found $n = 2.04 \pm 0.16$. Aristarkhova[17] reported that $n = 3.2$ on the basis of chemiluminescence from oxidizing ethylbenzene solutions containing E, and Niki recently estimated $n = 1.4$ in oxidizing ethylbenzene.[14]

We report here on a detailed study of the oxidation products of E with *tert*-alkylperoxy radicals and a direct measure of the radical scavenging efficiency, n, of E in acetonitrile and hexane at 50 °C.

Experimental Section

E purchased from Sigma (*dl*-α-tocopherol) or Eastman (*d*-α-tocopherol, 99%) was used. dl-α-Tocopherol was purified by HPLC before use. *d*-α-Tocopherol was used as received. Both compounds eluted as single peaks by HPLC and had identical UV extinction maxima and coefficients (λ_{max} 298 nm, hexane; $\epsilon_{298} = 3650 \pm 100$ M^{-1} cm^{-1}) in agreement with the literature.[18]

We used radical initiators azobis(*n*-butylcarboxypropane) (ABCP), and azobis(isobutyronitrile) (AIBN). ABCP was synthesized by the HCl-catalyzed butanolysis of AIBN.[19,20] Baker AIBN was recrystallized from ethanol.

Burdick and Jackson HPLC-grade hexane and acetonitrile were used as received.

For most experiments, reaction mixtures in hexane or acetonitrile containing constant initiator and varying amounts of E or BHT were simultaneously heated at 50.0 ± 0.1 °C in septum-sealed 4-mL vials. These vials were withdrawn at measured time intervals and analyzed by HPLC for antioxidant concentration.

For acetonitrile experiments, stock solutions of BHT and AIBN were prepared by weighing BHT and AIBN into tared volumetric flasks, which were then filled with solvent. A methanolic solution of E was blown dry with an argon stream and acetonitrile was added to make a stock solution of E. Portions of these stocks and makeup acetonitrile were added to the reaction vials to give 0.015 M AIBN and varying concentrations of E and BHT.

In hexane solvent all stocks were made with weighed amounts of E, BHT, or ABCP, which were again transferred in known amounts to the reaction vials. Other experiments were set up differently. E ($(2–4) \times 10^{-4}$ M in hexane) was assayed by UV spectroscopy, using $\epsilon_{298} = 3650 \pm 100$ M^{-1} cm^{-1}. Neat ABCP ($\epsilon_{363} = 20.0$ M^{-1} cm^{-1}) was added to the UV cuvette by a Pasteur pipet and the absorbance change at 363 nm was measured to vary [ABCP] between 2.6×10^{-3} and 2.9×10^{-2} M.

HPLC analysis of E and BHT was accomplished with a Waters chromatographic system with a 440 detector at 280 nm or a Schoeffel 770 detector at 293 nm, WISP auto sample injector, and 10-cm μ-C_{18} radial compression column. A 30-cm μ-C^{18} column used in some cases gave poorer resolution. Methanol at 2 mL/min was the eluting phase. Peak areas were determined with a Spectra Physics minigrator, and absolute concentrations of E and BHT were determined from calibration curves of area response vs. concentration.

α-Tocopherylquinone (**3**) was produced from E by oxidation with $FeCl_3$ in ethanol,[21] while tocopherol spiro dimer **4** was synthesized following the procedure of Nilsson and co-workers.[22] We analyzed **3** and **4** by HPLC, using the conditions described above for E and BHT. An eluting solvent of 50/50 methanol–ethyl acetate was used in the case of spiro dimer **4**.

We hydrolyzed HPLC-purified peroxycyclohexadienones **5a** and **5b** in methanol by adding 0.10 mL of 1 M HCl to 1-mL samples contained in UV cuvettes, after first recording the UV spectrum. Five minutes after addition of HCl, no more spectral changes were noted, and the spectrum of tocopherylquinone (**3**) was recorded. The presence of **3** was also verified by HPLC.

Hydrolysis and characterization of the peroxycyclohexadienone from 2,6-di-*tert*-butyl-4-methoxyphenol was performed on an ~10-mg sample in acetonitrile, using 1 M HCl. HPLC analysis of the peroxycyclohexadienone/phenol mixture before and after HCl treatment showed complete loss of the peroxy dienone peak and production of a new peak shown to be 2,6-di-*tert*-butyl-1,4-quinone by coelution with an authentic sample (Aldrich Chemical Co.) and from its UV spectrum (λ_{max} 320 nm, $\epsilon_{max} = 460$ M^{-1} cm^{-1}). Quantitation by peak area showed that 100% of 2,6-di-*tert*-butyl-4-methoxyphenol oxidized by $RO_2\cdot$ radicals gave the corresponding quinone after hydrolysis of the mixture.

Results and Discussion

Product Studies. Oxidized mixtures of E in hexane and acetonitrile showed that one major primary product peak formed as E disappeared. The product eluted after E on reverse-phase HPLC columns when ABCP was used as the $RO_2\cdot$ source and eluted before E when AIBN was used. At high HPLC resolution (10-cm column) each of these single-product peaks resolved into two peaks, presumably syn and anti isomers obtained by $RO_2\cdot$ addition on the same or opposite side of the chromanoxy ring relative to the phytyl chain. When collected by HPLC, these products showed absorbance maxima at 236 ± 3 nm (methanol) with shoulders at 290 nm. These spectra are very similar to those of the coupling product of *tert*-butylperoxy and 2,6-di-*tert*-butyl-4-methylphenoxy[23] or the *p*-hydroperoxycyclohexadienone reported by Clough et al.[24] formed by reaction of singlet oxygen and E. We have assigned the structures as **5a,b**.[8,12,25]

Compounds **5a** and **5b** decomposed rapidly to tocopherylquinone (**3**) in the presence of 0.1 M HCl. Assuming quantitative hydrolysis of these peroxy ketals to **3**, we calculate a molar extinction coefficient of 13 000 ± 2000 M^{-1} cm^{-1} at 240 nm for **5a** and **5b** on the basis of a molar extinction coefficient of 19 400 for **3**.

Using this extinction coefficient, we estimate yields of the coupling products **5a** and **5b** from the ABCP and AIBN experiments to be only 30 ± 15% of E lost with ABCP and 50 ± 10% for AIBN although eq 1 and 2 predicts a 1:1 equivalence. This finding is consistent with a 50% yield of **3** based on E consumed following acid hydrolysis of **5a** or **5b**.

To confirm that hydrolysis of peroxy ketals like **5** give quantitatively the corresponding quinones under the conditions of our experiments, we oxidized 1×10^{-3} M 2,6-di-*tert*-butyl-4-methoxyphenol with excess $RO_2\cdot$ derived from AIBN at 50 °C in acetonitrile. HPLC analysis showed only one product peak at ~50% conversion, which was rapidly and quantitatively (based on consumed phenol) transformed to the corresponding quinone on treatment with dilute HCl at 25 °C.

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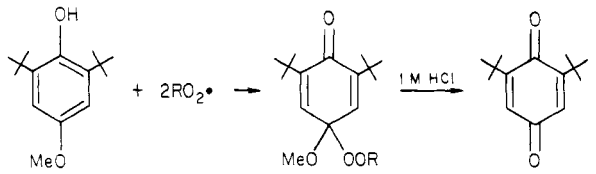
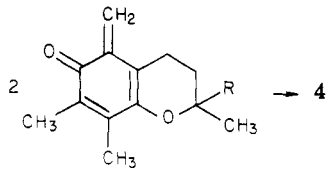
(25) We have been unable thus far to isolate the peroxycyclohexadienone in sufficient purity and quantity to measure the NMR spectrum or the C, H, O content.



Clearly peroxy ketals **5a** and **5b** cannot be the only products, and we do note that two other product peaks elute close to that to the peroxy ketal. However these peaks do not correspond to other reported oxidation products of E. Neither spiro dimer[22,26] **4**, produced from α-chromanoxy disproportionation[27] (reaction 5), nor α-tocopherylquinone[18,22] (**3**) could be detected in reaction mixtures. This was established by injecting known amounts of authentic samples of **3** and **4**. There are literature reports, however, that **4** is not stable in the presence of E but it reduces to di-γ-tocopherylethane.[28-30] That significant amounts of **4** are produced and then destroyed by reaction with E in hexane cannot be discounted because such reactions would lower n from 2 (see below). However, we found no loss on heating E with **4** in acetonitrile. Spiro dimer **4** can be formed via cyclodimerization of the quinomethide **6**, and quinomethide can be formed,



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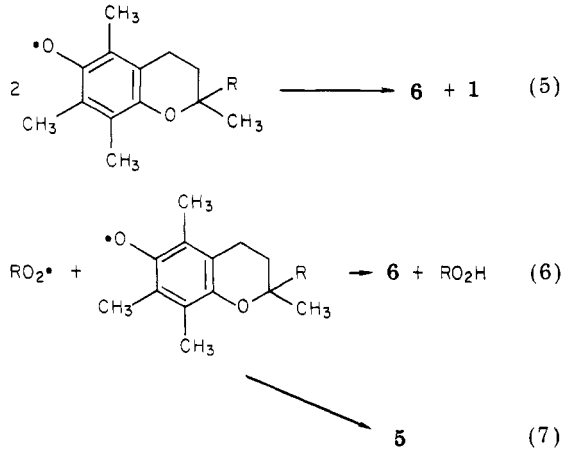
in turn, by disproportionation of two chromanoxy radicals (reaction 5) or by disproportionation of chromanoxy and $RO_2\cdot$ (reaction 6).



To test for the intervention of reactions **4** or **5**, which would account for the missing E· radicals, we measured the yield of peroxy ketal **5** as the concentration of E was increased six fold from 0.4 to 2.5 mM with constant ABCP. No significant change in peroxy ketal nor other product peaks was found (one isomer appeared to decrease by 30%), which leads us to conclude that reaction 5 probably is unimportant but that reaction 6 or its kinetic equivalent (such as addition of RO_2 at the ortho carbon) is responsible for missing E. Acid treatment of the product mixture led to rapid loss of peroxy ketals but no significant change in the composition of other product peaks. We believe this observation rules out quinomethide since this product should protonate and hydrolyze as well and suggests that the products are ortho peroxy adducts **7**.

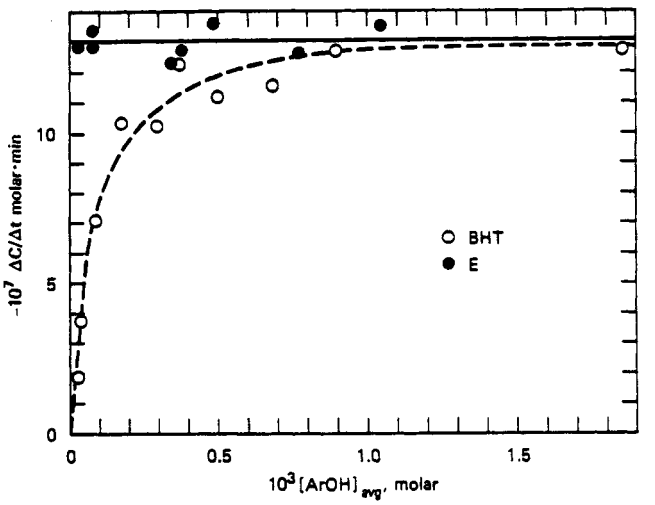
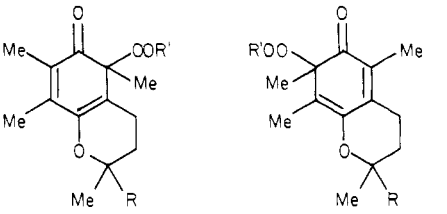


Figure 1. Rate of concentration change of BHT or E as a function of average concentrations in acetonitrile containing 0.015 M AIBN.



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Kinetic Studies. To measure the radical scavenging efficiency of E ($\Delta RO_2/\Delta E$) designated n, we used 4-methyl-2,6-di-*tert*-butylphenol (BHT), which has $n = 2$,[6,7] to measure production of $RO_2\cdot$ from 0.0015 M AIBN solutions in acetonitrile at 50 °C. To verify that sufficient BHT was present to trap all $RO_2\cdot$ and prevent their self-termination, we changed the starting BHT concentration while keeping AIBN concentration constant and measured the BHT loss rate. We found that at high initial concentrations of BHT, $\Delta BHT/\Delta t$ was independent of [BHT]. However, below 1×10^{-3} M BHT, the $RO_2\cdot$ scavenging efficiency decreased; at 1×10^{-4} M BHT only half the $RO_2\cdot$ (based on the maximum rate) was scavenged and at 3×10^{-5} M BHT only one $RO_2\cdot$ radical in ten was scavenged. Figure 1 illustrates this behavior and Table I summarizes the data.

On the other hand, E did not show any loss of scavenging efficiency over this same concentration range. Solutions containing 4×10^{-5} M E showed the same consumption rate as solutions containing 1×10^{-3} M E, within experimental error (Table I and Figure 1). This is consistent with the large H-atom transfer rate constant (k_1) reported for E.[15]

The average of all E experiment results gave a loss rate for E of 2.17 ± 0.08 M s^{-1}, which is marked by the limit line in Figure 1. The BHT data converge to this limit, which indicates that E and BHT have the same stoichiometry for scavenging $(CH_3)_2C(CN)OO\cdot$ and $n = 2$ for E.

We verified this conclusion by reacting AIBN with E and BHT in separate tubes at 50 °C over a 24-h period. The starting concentrations of E and BHT were 2.0×10^{-3} M

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Table I. Concentration Dependence of BHT and E Oxidation Rates at 50 °C in Acetonitrile Containing 0.015 M AIBN[a]

ArOH	time, min	$10^4[ArOH]_0$	$10^4[ArOH]_t$	$10^4[ArOH]_{av}$	$10^9(\Delta[ArOH]/\Delta t)$ M s^{-1}
BHT	35	0.281	0.216	0.249	3.10
	35	0.413	0.330	0.371	6.33
	35	0.956	0.709	0.832	11.8
	35	1.82	1.46	1.64	17.3
	140	3.65	2.21	2.93	17.2
	35	3.84	3.41	3.63	20.7
	140	5.78	4.21	4.99	18.7
	140	7.69	6.06	6.87	19.3
	140	9.84	8.04	8.94	21.3
	140	19.4	17.6	18.5	21.3
E	35	0.550	0.099	0.325	21.5
	35	1.01	0.560	0.780	21.5
	3	1.08	0.611	0.846	22.3
	35	3.74	3.31	3.53	20.5
	140	3.75	1.97	3.86	21.3
	140	5.85	3.94	4.90	22.7
	140	8.70	6.93	7.81	21.2
	140	11.3	9.48	10.4	22.5
			average of E experiments		21.7×10^{-9} M s^{-1}

[a] All concentrations are molar.

Table II. Limit Oxidations of BHT and E at 50 °C in Acetonitrile Containing 0.015 M AIBN[a]

ArOH	time, min	$10^3[ArOH]$, M	$-10^3\Delta[ArOH]$, M
BHT	0	2.11	0
	180	1.88	0.23
	480	1.54	0.58
	1020	0.85	1.26
	1275	0.56	1.55
E	0	1.89	0
	180	1.62	0.27
	480	1.26	0.63
	1020	0.53	1.35
	1275	0.22	1.67

[a] Concentrations were chosen to trap all RO_2.

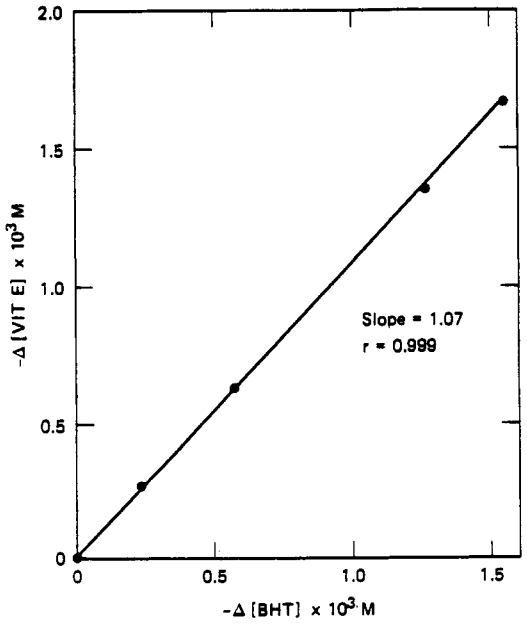

Figure 2. ΔE vs. ΔBHT in acetonitrile with 0.015 M AIBN at 50 °C, $[E]_0 = [BHT]_0 = 2$ mM.

each, while the initial concentration of AIBN again was 0.015 M. We analyzed for E and BHT at several times and then plotted $-\Delta[E]$ vs. $-\Delta[BHT]$ (Figure 2). The 1.07 ± 0.01 slope shows an identical stoichiometry. We calculate $n = 1.87 \pm 0.02$ in close agreement with Burton and Ingold.[15] Table II summarizes the data.

This latter set of experiments was repeated in hexane, using the initiator azobis(2-(*n*-butylcarboxy)propane) (ABCP), which is more soluble than AIBN. When hexane solutions containing 2×10^{-3} M BHT or E and 0.015 M

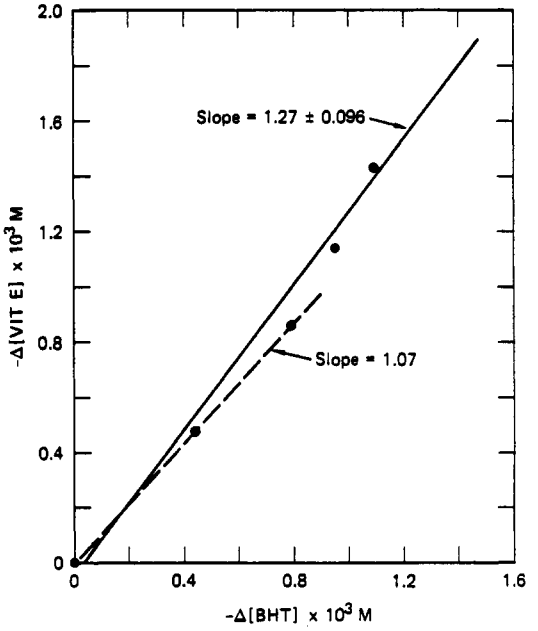

Figure 3. Δ[vit E] vs. Δ[BHT] with 0.015 M ABCP in hexane at 50 °C, $[E]_0 = [BHT]_0 = 2.00$ mM.

Table III. Limit Oxidations of BHT and E at 50 °C in Aerated Hexane Containing 0.015 M ABCP[a]

ArOH	time, min	$10^3[ArOH]$, M	$-10^3\Delta[ArOH]$, M
BHT	0	2.04	0
	480	1.59	0.45
	960	1.25	0.79
	1200	1.09	0.95
	1440	0.95	1.09
E	0	2.03	0
	480	1.55	0.48
	960	1.17	0.86
	1200	0.88	1.14
	1440	0.60	1.43

[a] Phenol concentrations were chosen to trap all RO_2.

ABCP were decomposed in parallel at 50 °C, E was lost no more quickly than BHT at low conversions (Figure 3 and Table III). A plot of $-\Delta$[E] vs. $-\Delta$[BHT] had an initial slope of 1.07 ± 0.09, which gives n = 1.86 ± 0.1 in good agreement with the result in acetonitrile. A least-squares regression of all data gave n = 1.6 ± 0.2. Varying [ABCP] over the range 2.5×10^{-3} to 2.8×10^{-2} did not affect n when [E] ranged from 2×10^{-4} M to 4×10^{-4} M.

Conclusion

Oxidation of E by peroxy radicals follows the same pathway found for other hindered phenols, but the chemistry is more complicated than for 2,6-di-*tert*-butyl phenols because about half the interactions between E· and RO_2· lead to products other than peroxy ketal **2**, probably addition at *o*-methyl positions. Neither dimers nor tocopherylquinone were observed in our studies, and their reported occurrence probably reflects special conditions of one-electron oxidation by metal ions or, in the case of tocopherylquinone, subsequent hydrolysis of initially formed peroxy ketal. We should note that RO_2· oxidations of E sequestered in phosphatidylcholine bilayers suspended in pH 7 buffer solutions gave only tocopherylquinone in about 25% yield. One explanation is that water intrudes into the bilayer no promptly hydrolyze the peroxy ketal. Another possibility is that peroxy radicals (generated from lipophilic ABCP) and E· interact at or near the polar head groups of the lipid, and thus peroxy ketal is readily exposed to hydrolytic conditions.[31]

The close agreement between two kinds to measurements for n gives us confidence in the value of 2 as an accurate measure of the stoichiometry of the E + RO_2· interaction and reaffirms our conclusion that all of the oxidized E ultimately binds with RO_2. Our experiments do not provide a measure of k_1 directly but do demonstrate that E is much more reactive with RO_2· than ordinary phenols as was previously determined by Niki[14] and Burton and Ingold.[15] We estimate $k_1 > 2 \times 10^5$ M^{-1} s^{-1}.

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Registry No. *d*-**1**, 59-02-9; *dl*-**1**, 10191-41-0; *d*-**3**, 7559-04-8; **4**, 1604-73-5; **5a**, 88056-74-0; **5b**, 88083-17-4; **7** (R′ = C(CN)$(CH_3)_2$) (isomer 1), 88056-75-1; **7** (R′ = C(CN)$(CH_3)_2$) (isomer 2), 88056-76-2; **7** (R′ = $(CH_3)_2$CCOOBu) (isomer 1), 88056-77-3; **7** (R′ = $(CH_3)_2$CCOOBu) (isomer 2), 88056-78-4; ABCP, 21302-38-5; AIBN, 78-67-1; 2,6-di-*tert*-butyl-4-methoxyphenol, 489-01-0; 2,6-di-*tert*-butyl-*p*-quinone, 719-22-2.

(31) Barclay et al.[32] have shown that inhibition of methyl linoleate oxidation by E in micelles is significantly enhanced by ascorbic acid in the aqueous phase.

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Chemical Behavior of Cyclopropylmethyl Radicals: Relative Unimportance of Cyclopropylmethyl to 3-Butenyl Rearrangement in the Cycloaddition Reactions Proceeding via Allylically Stabilized Diradicals[1a]

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The reaction of *cis*-1-cyclopropyl-1,3-butadiene (**1c**) with fluorenylidene (Fl:), which was thermally generated from 9-diazofluorene (**2**), produced **3c** in addition to fluorenone azine (**4**) and 9,9′-bifluorenylidene (**5**). The reaction of **1t** with **2** gave a mixture of two adducts, **3t** and **6**, in which **6** was proved to be the secondary product derived from **3t**. The addition of Fl: was thus regiospecific and gave **3**, and the stereochemistry of the C1–C2 double bond in **1** was retained throughout the addition. The reaction of 1,1-dicyclopropyl-1,2-propadiene (**7**) with Fl: took place exclusively at the C2–C3 double bond in **7** to give **8**, whereas dibromocarbene attacked **7** exclusively at the C1–C2 double bond to give **13**. On being heated at 140 °C, **13** underwent the anticipated skeletal isomerization to give **14**. At 180 °C, more extensive rearrangements took place to produce **15**, **16Z**, and **16E** in a 2.9:1.0:3.7 ratio. 1,1-Dibromo-2,2-dicyclopropylcyclopropane (**19**), on the other hand, produced a mixture of **20Z** and **20E** on being heated at 140 °C. In contrast to the results obtained in the Fl: addition reactions, the radical addition of bromotrichloromethane (**22**) to **1** yielded cyclopropane-cleaved **23** as the exclusive product. It may thus be concluded that the cyclopropylmethyl to 3-butenyl rearrangement in the diradicals, in which the cyclopropyl-substituted site is stabilized with allylic resonance, is unimportant relative to the intramolecular coupling of the two radical sites at least at 140 °C or below, whereas the intermolecular atom abstraction of the cyclopropyl-substituted allyl radical occurs relatively slowly and hence is accompanied by the cyclopropane cleavage.

Some time ago, we[2] demonstrated that cyclopropyl-substituted ethylene is a valuable substrate to investigate radical cycloadditions. It was observed that the addition, which proceeded in a stepwise fashion via a diradical intermediate, yielded a significant amount of cyclo-

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