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Vitamin E Chemistry. Studies into Initial Oxidation Intermediates of α-Tocopherol: Disproving the Involvement of 5a-*C*-Centered "Chromanol Methide" Radicals

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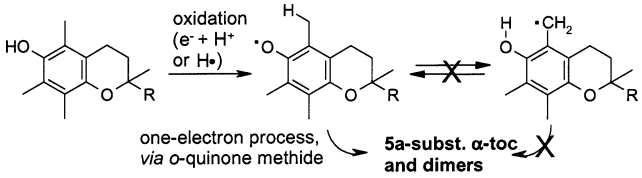

Contrary to concepts handed down in the literature from the early days of vitamin E research, one-electron oxidation of vitamin E does not involve 5a-*C*-centered radicals. A combined approach of analytical techniques, in particular electron paramagnetic resonance spectroscopy (EPR), organic synthesis of special derivatives, isotopic labeling, kinetic studies, and computational chemistry was used to re-evaluate the one-electron and two-electron oxidation chemistry of α-tocopherol (α-toc). EPR in combination with 5a-^{13}C-labeled compounds provided no indication of the involvement of 5a-*C*-centered radicals. Oxidation of special tocopherol derivatives were used to disprove the occurrence of 5a-*C*-centered one-electron intermediates. Additionally it was shown that those vitamin E reactions that were commonly evoked to plead for the involvement of *C*-centered tocopheryl radicals actually proceeded via heterolytic, i.e., non-radical, intermediates. The results will help to clear widely spread misunderstandings about the chemistry of vitamin E and will have mechanistic implications for the synthesis of tocopherol-based supramolecular structures and 5a-substituted α-tocopherol derivatives.

1. Introduction

Vitamin E, first reported barely one century ago, is the biologically most important fat-soluble antioxidant and has become a commodity product and bulk chemical in the meantime. The major, large-scale application of vitamin E is animal nutrition, and many pharmaceutical, health care, and cosmetic products contain the substance. In the consumer notion vitamin E is connected with terms such as antioxidant, radical scavenging, and anti-aging. Usually, and due to the dominance of the α-homologue in all kinds of applications, the term vitamin E is widely used synonymous with α-tocopherol or even α-tocopheryl acetate, but in fact it is a generic descriptor of all tocol and tocotrienol derivatives exhibiting qualitatively the vitamin E activity (as determined by specific biological tests) of α-tocopherol,[1−4] i.e., covering the four tocopherols and the four tocotrienols (α-, *β*-, *γ*-, and *δ*-homologues).

Many reports on vitamin E chemistry date back to the 1950s to 1970s of the 20th century, and most of them are dealing with α-tocopherol chemistry or with converting non-α-tocopherols

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into the α-congener. After that time, the research focus shifted somewhat to biological and medicinal aspects of tocopherols. The chemical basics were largely handed down from that time and after some time were seen as well established. As an example, the peculiar reactivity of the 5-methyl group in α-tocopherol (**1**) had been explained by the ill-defined and inapplicable Mills−Nixon effect[5] for more than six decades. Nowadays, the matter finally has been clarified, and this hypothesis was replaced by the modern strain-induced bond localization (SIBL) explanation.[6,7]

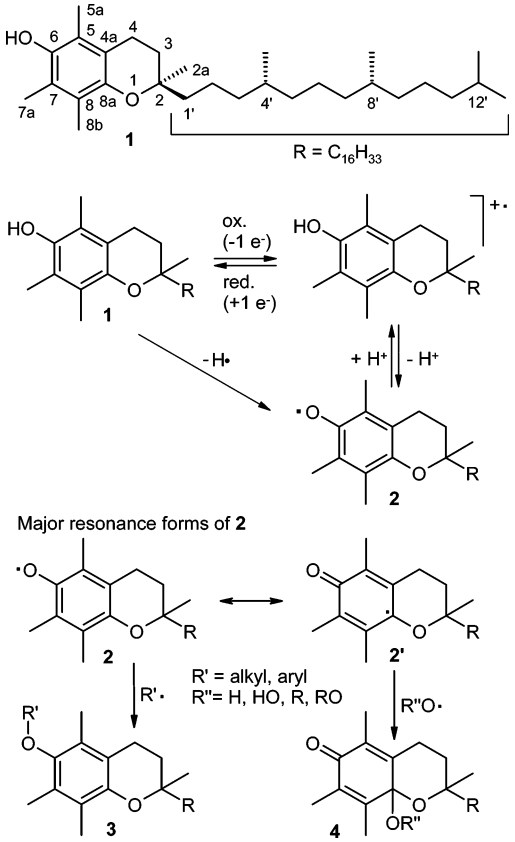
The fact that the interest in tocopherols shifted away from purely chemical aspects may also explain why theories and reactions that might appear questionable today were passed around for a longer time by citation, rewriting, and incorporation into reviews.

This paper is concerned with a particular aspect of vitamin E chemistry or, correctly, α-tocopherol chemistry: the nature of primary intermediates in the one-electron oxidation of the compound, i.e., α-tocopherol-derived radicals. In particular, the involvement of *C*-centered radicals at 5a-C is critically studied. Participation of 5a-C in radical processes was proposed in the early years of vitamin E chemistry and has become widely spread and accepted since then, not by appearance of additional proofs but by repeated citation and the lack of necessity to recheck that chemistry in detail. With the use of α-tocopherol and α-tocopherol-type model compounds in supramolecular chemistry and in 5a-*C*-linked derivatives, the question of the exact chemistry of early α-tocopherol oxidation intermediates became of crucial interest. In the present study, we set out to clarify that chemistry by a combined experimental and theoretical approach, applying electron paramagnetic resonance spectroscopy (EPR) and other analytical techniques, as well as synthesis of special derivatives, isotopic labeling, kinetic studies, and computational chemistry.

2. Results and Discussion

2.1. α-Tocopherol and Its Primary Oxidation Products−the Alleged Involvement of 5a-*C*-Centered Radicals. The chromanoxyl radical **2** is the primary homolytic (one-electron, radical) oxidation product of α-tocopherol (**1**). Its formation and occurrence is comprehensively supported and confirmed by EPR[8−14] and ENDOR[15] experiments. Radical **2** can be formed by two pathways (Scheme 1). The first one involves loss of a hydrogen atom and is largely dependent on the hydrogen atom

SCHEME 1. Structure and Atom Numbering of α-Tocopherol (1), Formation of the α-Tocopheroxyl Radical and Its Major Resonance Forms (2 and 2′), and Their Dominant Radical Coupling Products 3 and 4[a]



[a] Here and in the following the term "R = $C_{16}H_{33}$" refers to the (2*R*,4′*R*,8′*R*)-isomer.

acceptor. The second process involves one-electron oxidation to a radical cation, which can be observed by EPR spectroscopy at low temperatures under certain conditions,[15,16] followed by loss of a proton to form **2**. Also, the direct subsequent chemistry of the α-tocopheroxyl radical **2** is well established and no matter of debate. The spin density of **2**, as a classic phenoxyl radical, is mainly concentrated at oxygen O-6, which is the major position for coupling with other *C*-centered radicals, leading to chromanyl ethers **3**. The spin density is also increased at *ortho*- and *para*-positions (5-C, 7-C, 8a-C) of the aromatic ring. Coupling with other radicals, especially *O*-centered ones, proceeds mainly at the *para*-position (C-8a), leading to differently 8a-substituted chromanones **4** (Scheme 1).

The occurrence of a 5a-*C*-centered tocopherol-derived radical **5**, often called a "chromanol methide" radical, had been postulated in literature articles[17−24] dating back to the early days

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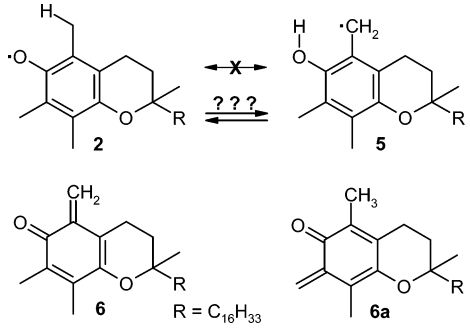
SCHEME 2. Structure of the Literature-Postulated 5a-*C*-Centered Radical 5 as a Tautomer of 2 and Structures of the "Favored" (6) and "Disfavored" (6a) α-Tocopherol-Derived *o*-Quinone Methides



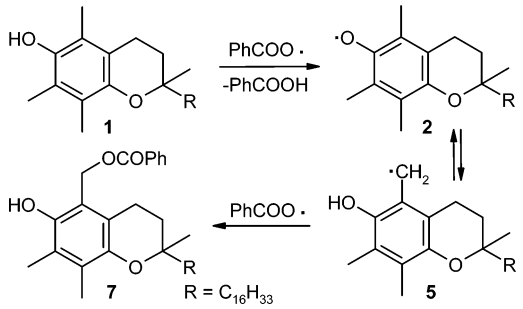
of vitamin E research, which have been cited or supposedly reconfirmed later.[25−28] In some accounts, this radical has been described in the literature as being a resonance form (canonic structure) of the tocopheroxyl radical, which of course is inaccurate. If indeed it exists, radical **5** represents a tautomer of chromanoxyl radical **2**, being formed by a chemical reaction, namely, a 1,4-shift of one 5a-proton to the 6-oxygen, and not just by a "shift of electrons" as in the case of resonance structures (Scheme 2).

In all accounts mentioning α-tocopherol-derived *C*-centered radicals, the spin density was described to be centered at 5a-C but not at alternative carbons, such as 7a-C or 8b-C. Actually, the occurrence of 5a-*C*-radicals was concluded from two facets of vitamin E chemistry: on the one hand by experimental observations that seemed to support 5a-*C*-radicals, and on the other hand by analogy to the chemistry of the α-tocopherol-derived *o*-quinone methide (oQM) **6**. These theoretical and experimental considerations will be briefly addressed next to explain the starting situation for our studies.

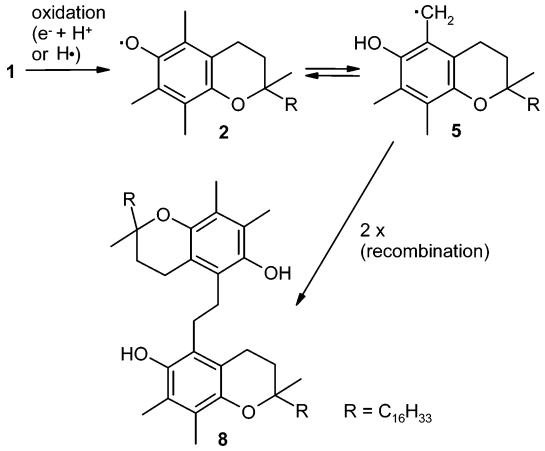
Alleged "Theoretical Evidence" for α-Tocopherol-Derived 5a-C-Radicals. *o*-Quinone methide **6**, a very frequent intermediate in tocopherol chemistry, is the product of two-electron oxidation processes. It is formed with large preference for 5a-C over 7a-C, oQM formation at the latter position leading to **6a** (Scheme 2). This peculiar reaction behavior of α-tocopherol has been attributed to the so-called Mills−Nixon effect. Even though this rationale was shown to be wrong and inapplicable to the α-tocopherol case,[6] it haunts the pertinent literature as a blurred theory accounting for the preference of 5a-C in all kinds of reactions. From the observed favoring of the 5a-methyl group over the 7a-methyl group upon formation of an *o*-quinone methide, it was concluded that for hypothetic α-tocopherol-derived *C*-centered radicals the situation must be similar: the radical was supposed to be preferentially centered at 5a-C and not at 7a-C.

Alleged "Experimental Evidence" for α-Tocopherol-Derived 5a-C-Radicals. Basically, three reactions were evoked to support the occurrence of 5a-*C*-centered radicals in tocopherol chemistry. The first one is the formation of 5a-substituted derivatives in the reaction of α-tocopherol with radicals and radical initiators. The most prominent example is here the reaction of **1** with dibenzoyl peroxide leading to 5a-α-tocopheryl benzoate (**7**) in fair yields,[17] so that a "typical" radical recombination mechanism was postulated (Scheme 3). Similarly, low yields of 5a-alkoxy-α-tocopherols were obtained by oxidation of α-tocopherol with *tert*-butyl hydroperoxide or other peroxides in inert solvents containing various alcohols ranging from methanol to cholesterol,[29,30] although the involvement of 5a-*C*-centered radicals in the formation mechanism was not evoked for explanation in these cases. Also, oxidation of α-tocopherol in the presence of methyl linoleate in methanol provided the 5a-methoxy derivative.[31]

SCHEME 3. Hypothetical Radical Mechanism for the Formation of 5a-α-Tocopheryl Benzoate (7) by Reaction of α-Tocopherol (1) with Dibenzoyl Peroxide



SCHEME 4. Formation of α-Tocopherol Ethano-dimer 8 as the Result of a Hypothetical Radical Recombination of Two Radicals 5



The second observation cited as evidence for a radical mechanism involving radical **5** is the frequent occurrence of ethano-dimer **8**, proposed to proceed by recombination of two 5a-*C*-centered radicals **5** (Scheme 4).[27,32,33]

The third fact that seemed to argue in favor of the occurrence of **5** was the observation that reactions of α-tocopherol under typical radical conditions, i.e., in the presence of radical initiators in inert solvents or under irradiation, provided also large amounts

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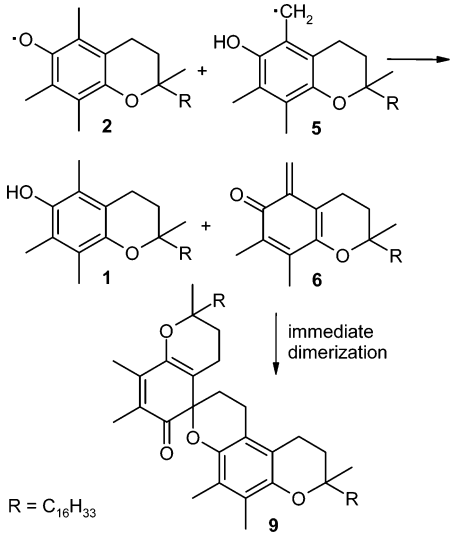
SCHEME 5. Hypothetical Disproportionation of Two α-Tocopherol-Derived Radicals 2 and 5 in the Absence of Other Coreactants To Account for the Formation of Typical Two-Electron Oxidation Products (α-Tocopherol Spiro-dimer 9)



of two-electron oxidation products such as oQM **6** and its spiro-dimerization product **9**.[21,32,33] This was taken as support of a disproportionation reaction involving tocopheroxyl radical **2** and its tautomer **5** (Scheme 5), affording one molecule of oQM **6** (oxidation) and regenerating one molecule of **1** (reduction). The term "disproportionation" was used here to describe a one-electron redox process with concomitant transfer of a proton, i.e., basically an H-atom transfer from **5** to **2**. In the following, we would like to present an EPR study combined with labeling experiments, which clearly speak against the involvement of 5a-*C*-centered radicals in tocopherol chemistry. This is followed by evidence for the non-radical course of the above reactions in Schemes 3−5 and explanation of their actual mechanism.

2.2. EPR, Computational, and Isotopic Labeling Study. From the above-mentioned experimental observations and theoretical considerations the question arises why 5a-*C*-centered radical **5**, if indeed in equilibrium with tocopheroxyl radical **2**, as often proposed, cannot be reported by EPR spectroscopy. In a first step, we approached this question by quantum chemical calculations.[34] The spin distribution data obtained by these calculations predicted high spin density for the phenolic oxygen atom of chromanoxyl radicals; however, this cannot be directly observed by EPR in natural ^{16}O compounds (see Table 1). Similarly high values were found for the carbon atoms of the aromatic ring, especially in *para*- and *ortho*-positions, which is in accordance with the observed chemistry, i.e., occurrence of coupling products at 6-O, 5-C, and 8a-C. The electron densities at all substituent positions, such as the three methyl groups 5a-CH_3, 7a-CH_3, and 8b-CH_3, as well as the methylene group 4-CH_2, are significantly lower. The hypothetic coupling values for ^{13}C atoms at the 5a, 7a, and 8b positions were predicted with 3.32, 2.53, and 0.68 G. Hydrogen coupling constants for the methyl groups, averaged by their free rotation, were found to be 6.49, 4.52, and 1.68 G for 5a-methyl, 7a-methyl, and 8b-methyl, respectively. Large hydrogen coupling constants in the methyl groups are associated with high spin densities at the respective methyl carbon atoms. The computational results show no evidence whatsoever for a special preference of 5a-C in forming a radical. The spin density values indicate where radical attack or recombination reactions will occur; for the methyl groups these processes mean H-atom abstraction. The H-atom abstraction will be favored in the order 5a-CH_3 > 7a-CH_3 ≫ 8b-CH_3 but will be rather unlikely as compared to reactions at 6-O and the aromatic ring carbons.

TABLE 1. Coupling Constants for Selected Positions in the Chromanoxyl Ring System Predicted by Computations on the B3LYP/6-31G(d,p) Level (Absolute Values)[a]

position	nucleus	coupling constants (G)
6a	^{17}O	10.81
5a	3 H (av)	6.49
5a	^{13}C	3.32
5	^{13}C	12.12
7a	3 H (av)	4.52
7a	^{13}C	2.53
7	^{13}C	8.66
8b	3 H (av)	1.68
8b	^{13}C	0.68
8	^{13}C	7.21
8a	^{13}C	13.90
4a	^{13}C	8.20

[a] In non-labeled compounds, only proton couplings are experimentally detectable by EPR spectroscopy.

H-atom abstraction from the 5a-methyl group in tocopheroxyl radical **2** would formally produce a biradical as a resonance form of oQM **6** but not the 5a-*C*-centered radical **5**, which has an intact phenolic OH group. Radical **5** would rather be formed by a tautomerism, i.e., a proton shift from the methyl group to the oxygen, a [1,4]-sigmatropic proton shift that proceeds via a cyclic transition state according to a concerted mechanism. Computations readily showed that radical **5** was energetically largely disfavored as compared to tocopheroxyl radical **2** by 0.029 H (78.10 kJ mol^{-1}). This is in accordance with the EPR results (see below) that provided no evidence as to the presence of *C*-centered radicals, by giving the neat phenoxyl spectrum of **2**. However, the occurrence of **5** in small amounts and very low steady-state concentrations cannot be excluded just from this observation.

Moreover, computations and theoretical considerations provided clear evidence against a preference of position 5a over position 7a as radical **2** is still an *aromatic* system. The radical centered at 5a-C (structure **5**) was calculated to be only insignificantly more stable by 1.55 kJ mol^{-1} than the one centered at 7a-C (structure **5a**). In contrast, in the case of the *quinoid* oQM structures the involvement of 5a-C in oQM formation is clearly energetically favored over 7a-C (and of course over 8b-C). This was demonstrated experimentally and smoothly explained by the strain-induced bond localization (SIBL) approach[6] (Scheme 6). Further confirmation comes from computational results showing the 5a-oQM (**6**) to be more stable by 21.65 kJ/mol than the 7a-oQM (**6a**). This clearly proved that the conclusion by analogy as described in the introductory section is wrong: the observed and experimentally well-documented favoring of the 5a-C position in the formation of *o*-quinone methides, i.e., *quinoid* structures as the result of a *two-electron oxidation*, does not allow the conclusion that the situation is similar for hypothetic α-tocopherol-derived *C*-centered radicals, i.e., *aromatic radical* structures resulting from *one-electron* oxidation. Thus, there are no theoretical consid-

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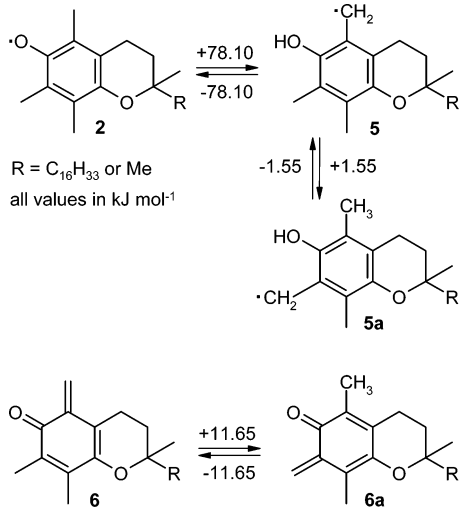
SCHEME 6. Comparison of Computational Data (Δ*E*, kJ mol^{-1}) for the Two Tautomeric *o*-Quinone Methides (6 and 6a) and the Hypothetic Two Tautomeric Radicals (5 and 5a) Derived from the α-Tocopherol Model Compound 2,2,5,7,8-Pentamethylchroman-6-ol (PMC, R = Me)[a]



[a] The data for the analogous species derived from α-tocopherol (**1**) can be assumed to be nearly identical, since the influence of the side chain is effectively cancelled out in relative values.

erations supporting a dominance of radical **5** over the analogous radical at 7a-C, contrary to the above-mentioned conventional notion.

Thus, if radicals at 5a-C and 7a-C are involved in tocopherol chemistry, then products of both species would have to be expected. The fact that in reality products of 5a-C are highly preferred over those of 7a-C can already be seen as an indirect proof of the underlying chemistry not being radical by nature.

To verify the theoretical predictions experimentally, we synthesized α-tocopherol (**1**, 2*R*,4′*R*,8′*R* stereoisomer) ^{13}C-labeled at either 5a-C (**1*-5a**) or 7a-C (**1*-7a**) and also the 5a-^{13}C-labeled derivative (**PMC*-5a**) of its truncated model compound 2,2,5,7,8-pentamethylchroman-6-ol (**PMC**) (see Figure 1 and Experimental Section). The syntheses involved a Mannich reaction with ^{13}C-paraformaldehyde and morpholine leading to the 4-morpholino-(^{13}C-methyl) derivatives which were subsequently reduced by $NaBH_3CN$ to the ^{13}C-methyl products.

From the labeled compounds the corresponding radicals were generated by flash photolysis in benzene. The spectra of the 5a-^{13}C-labeled radicals in comparison to non-labeled material are shown in Figure 1.

The comparison of the spectra clearly showed the additional coupling of the ^{13}C atom in the labeled derivatives, and otherwise slightly different sets of coupling constants, which required detailed examination. For the analysis of the EPR spectra, the WINSIM program was used,[35] which iteratively optimizes the coupling constants using the values from quantum chemical calculations as starting conditions. The quality of the obtained fits was assessed by regression coefficients calculated by the simulation program. For labeled and unlabeled tocopheroxyl and chromanoxyl radicals the data are given in Table 2.

For non-labeled α-tocopherol and non-labeled PMC radicals characteristic couplings were found with the 5a-, 7a-, and 8b-

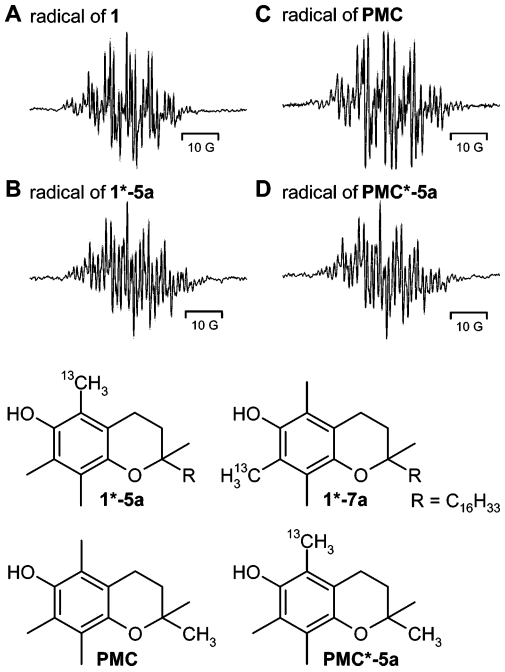


FIGURE 1. ^{13}C-Labeled and non-labeled starting phenols and EPR spectra of the respective phenoxyl radicals generated from 200 mM phenol solutions in benzene by flash photolysis: (A) non-labeled α-tocopheroxyl (**2**) from **1**; (B) 5a-^{13}C-labeled α-tocopheroxyl from **1*-5a**; (C) non-labeled pentamethyl-chromanoxyl from PMC; (D) 5a-^{13}C-labeled pentamethylchromanoxyl from **PMC*-5a**.

TABLE 2. Coupling Constants for the Hyperfine Splitting of EPR Spectra from ^{13}C Labeled and Non-labeled α-Tocopherol (Chromanol) Compounds

set	spin	no. of spins	**2**	5a-^{13}C-**2**	7a-^{13}C-**2**	PMC$^{\bullet}$	5a-^{13}C PMC$^{\bullet}$
1	0.5	3	6.016	5.835	5.912	6.009	5.817
2	0.5	3	4.527	4.541	4.498	4.627	4.542
3	0.5	3	0.942	0.912	0.919	0.983	0.881
4	0.5	1	1.463	1.419	1.246	1.553	1.407
5	0.5	1	1.435	1.558	1.538	1.552	1.561
6	0.5	1	0.057	0.984	0.929	0.110	1.016
R			0.917	0.922	0.753	0.987	0.925

methyl groups, as well as with the benzylic 4-CH_2 group of the pyrano ring, which is in agreements with previous findings.[36] Analogous experiments with the ^{13}C-labeled compounds resulted in almost identical coupling constants for those groups. However, because of the additional coupling of the ^{13}C atom with its nuclear spin of $^1/_2$, a changed hyperfine splitting was observed and iteratively calculated (Figure 1B and D; see also Table 2). The additional coupling constant amounted to about 1 G irrespective of whether the 5a- or the 7a-position had been labeled. To perform spectral simulations with a uniform set of coupling nuclei, an additional hypothetic coupling was introduced also for non-labeled compounds. The respective simulations always converged to values close to 0 G for this additional coupling, proving its absence in unlabeled compounds and thus confirming our assignment. As expected, the spin distribution at other positions of the molecule is nearly unaffected by the labeling. The quantum chemical calculations predict for both positions 5a-C and 7a-C considerably higher coupling constants

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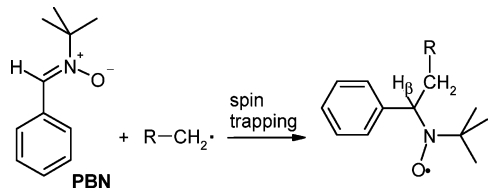
SCHEME 7. General Mechanism for the Spin Trapping of *C*-Centered Radical Species (Primary Alkyl Radicals) by PBN[a]



[a] The hyperfine structure of the spin adducts is usually dominated by the coupling of the β-proton and of nitrogen.

than experimentally observed, this discrepancy probably being related to the basis set chosen, which was not especially optimized for calculations of hyperfine couplings.

To verify the hypothetic involvement of *C*-centered radicals arising from α-tocopherol or PMC, the spin trapping technique in combination with EPR was employed. It is well-known that nitroxide spin traps efficiently scavenge *C*-centered radicals in the absence of oxygen. For the reaction of aliphatic carbon-centered radicals with the spin trap *N-tert*-butyl-α-phenyl-nitrone (PBN), high rate constants of about 10^7 L mol^{-1} s^{-1} were reported.[37] Also the formation of PBN spin adducts with aromatic *C*-centered radicals is evident from the numerous reports on spin adducts of phenyl radicals.[38−40] So far no PBN adducts with chromanoxyl radicals have been described. Therefore, if *C*-centered α-tocopherol-derived or PMC-derived radicals are produced in the presence of PBN, it is safe to assume that they would be efficiently trapped (cf. Scheme 7). Moreover, if the 5a-*C*-centered radical **5** indeed existed in a tautomeric equilibrium with the tocopheroxyl radical **2**, trapping products of **5** would accumulate as the radical is constantly removed out of the equilibrium by trapping and regenerated according to the equilibrium constant.

The trapping experiment was performed by irradiating a solution of PMC in benzene in either the presence or absence of PBN as the spin trap inside the cavity of the EPR spectrometer. In the first phase, a flash before each EPR scan was triggered until steady state was reached after about 90 s. Subsequently, the decay of the chromanoxyl radical was observed without irradiation (Figure 2). The decay curves were identical within the error limits of the measurement, independent of the presence or absence of PBN. Analysis of the half-lives of the corresponding decay curves by a simple first-order decay model gave half-lives of 37.2 ± 2.0 s for PMC alone and 35.0 ± 2.5 s for PMC with equimolar amounts of PBN present, the decay rates measured in three sets of experiments being statistically identical. In addition, after the complete decay of the chromanoxyl radical, no PBN spin adduct of carbon-centered radicals was observed (spectra not shown), although such adducts are known to have long half-lives of hours and even days.[41] In the presence of carbon-centered radicals, the corresponding spin adducts should have been readily detectable, and

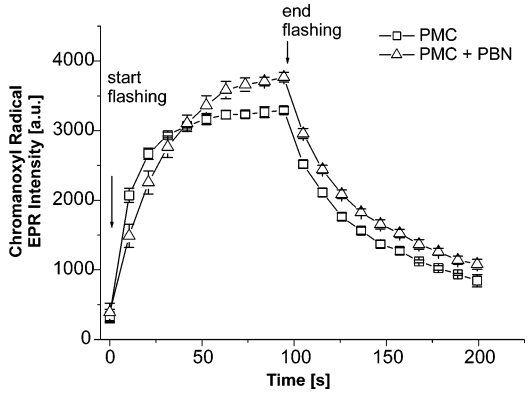
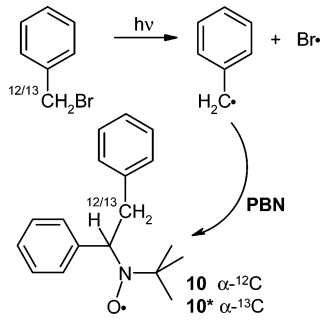


FIGURE 2. Formation and decay of chromanoxyl radicals formed from PMC by flash photolysis in benzene. The experiment was performed with 33 mM PMC alone (□) or with 33 mM PMC and 33 mM PBN together (△). Each data point is a mean ± SD of three separate measurements.

SCHEME 8. Photolysis of Benzyl Bromide (α-^{13}C-Benzyl Bromide) in the Presence of PBN in Benzene and Formation of the Corresponding Benzyl Radical Adducts (10 and 10*, Respectively)



the decay curves should show significant differences, with the decay of the chromanoxyl being noticeably accelerated by the trap constantly removing the *C*-centered radical out of the equilibrium with the chromanoxyl radical. Thus, the findings lead to the conclusion that carbon-centered chromanol radicals do not exist in equilibrium with the chromanoxyl radical. However, to make this argumentation safe and secure, it must be demonstrated that such 5a-*C*-centered radicals can indeed be trapped readily by PBN once they are formed. Only in this case can the absence of trapping products really be taken as proof of absence of the underlying radicals.

To address the topic of detectability of *C*-centered radicals derived from PMC or α-tocopherol by PBN trapping, the generation of the radical species under similar reaction conditions, i.e., by flash photolysis in benzene at ambient temperature, was required. In a first step, benzyl bromide was employed as a rather simple model compound with a photolabile bond for carbon (benzyl) radical formation. Despite its structural simplicity, the model possesses the basic structural elements of radical **5**: the aromatic nucleus and a benzylic position to simulate the 5a-position in α-tocopherol/PMC (Scheme 8).

The EPR spectra obtained by photolysis of benzyl bromide in the presence of PBN are shown in Figure 3A. The simulation of the respective hyperfine splitting of the benzyl radical adduct of PBN (**10**) gave a_N = 14.480 ± 0.014 G, $a_{H\beta}$ = 2.455 ± 0.021 G, and $a_{1/2}$ = 0.124 ± 0.009 G (n = 2). Repetition of the experiment with α-^{13}C-labeled benzyl bromide afforded the corresponding labeled adduct **10*** (Figure 3B), the coupling

(37) Greenstock, C. L.; Wiebe, R. H. *Can. J. Chem.* **1982**, *60*, 1560−1564.
(38) Janzen, E. G.; Coulter, G. A.; Oehler, U. M.; Bergsma, J. P. *Can. J. Chem.* **1982**, *60*, 2725−2733.
(39) Kandror, I. I.; Gasanova, R. G.; Freidlina, R. K. *Tetrahedron Lett.* **1976**, *14*, 1075−1078.
(40) Alekperov, G. A.; Zubarev, V. E.; Slovetskii, D. I. *Khim. Vys. Energ.* **2006**, *13*, 188−189.
(41) Janzen, E. G.; Chen, G.; Bray, T. M.; Reinke, L. A.; Poyer, J. L.; McCay, P. B. *J. Chem. Soc., Perkin Trans. 2* **1993**, *11*, 1983−1989.

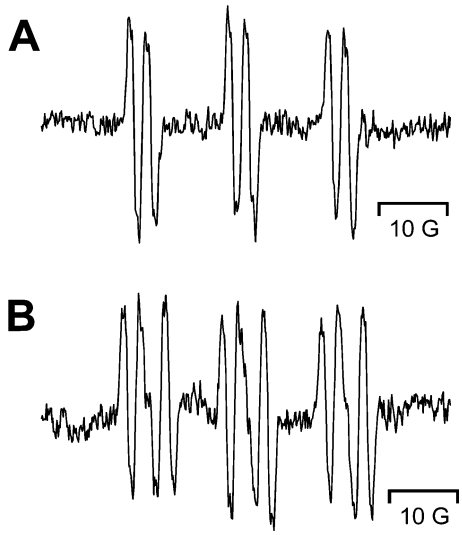
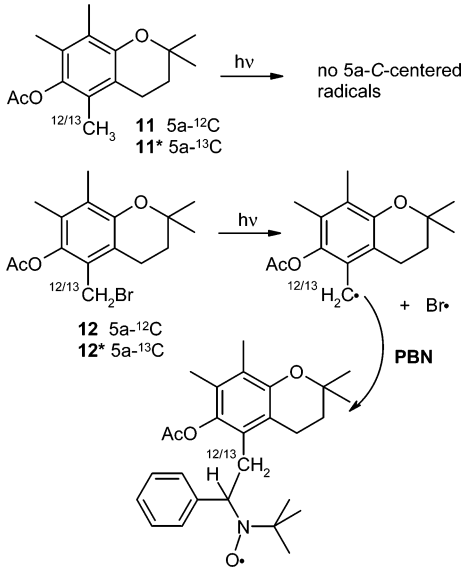


FIGURE 3. EPR spectra of spin adducts obtained upon UV irradiation of benzyl bromide (900 mM) and PBN (100 mM) in benzene using 310 nm cut off filter: (A) adduct from benzyl bromide (**10**); (B) adduct from α-^{13}C-benzyl bromide (**10***).

SCHEME 9. PBN-Trapping of 5a-*C*-centered Radicals Generated by Photolysis of the Corresponding 5a-Bromo-derivatives (12, 12*) and Lack of Radical Generation from the Phenyl Acetates (11, 11*)



constants being $a_N = 14.497 \pm 0.016$ G and $a_{H\beta} = 2.443 \pm 0.012$ G with an additional coupling constant $a_{13C} = 3.614 \pm 0.008$ G ($n = 2$). From these coupling constants and also from the simple appearance of the spectra, the effect of the labeling became obvious. The data unambiguously demonstrated the formation of a *C*-centered radical, the benzyl radical, under the conditions chosen.

This approach toward identification of *C*-centered radicals was transferred to the phenolic compounds of interest. For this purpose, the *O*-acetyl derivatives of non-labeled and labeled PMC (**11** and **11***, respectively) were synthesized by acid-catalyzed esterification with acetic anhydride. Similarly, the 6-*O*-acetyl-5a-bromo derivative of PMC (Scheme 9) was synthesized, both with natural isotopic composition at 5a-C (**12**) and 5a-^{13}C-labeled (**12***). In a first step, PMC was quantitatively converted into 5a-bromo-PMC by treatment with elemental bromine according to a non-radical, two-step oxidation-addition mechanism.[42] The bromo derivative was subsequently acetylated with acetic anhydride under acid catalysis.

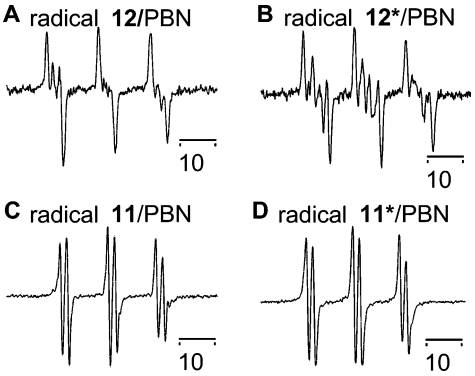


FIGURE 4. EPR spectra of spin adducts obtained from the UV irradiation of chromanol derivatives in the presence of PBN (100 mM) in benzene: (A) 630 mM **12**, (B) 630 mM **12***; (C) 630 mM **11**; (D) 630 mM **11***.

TABLE 3. Coupling Constants of PBN Spin Adducts Obtained from UV Irradiation of Labeled and Non-labeled Chromanol Derivatives[a]

	a_N (g)	$a_{H\beta}$ (G)	$a_{1/2,other}$ (G)	$a_{1/2,other}$ (G)
12	14.765 ± 0.007	2.365 ± 0.007	1.229 ± 0.013	0.066 ± 0.076
12*	14.585 ± 0.021	1.950 ± 0.042	0.930 ± 0.000	3.969 ± 0.042
11	13.628 ± 0.004	1.907 ± 0.037		
11*	13.627 ± 0.017	1.881 ± 0.050		

[a] All data are means ± standard deviation of 2-3 independent experiments.

Upon irradiation of these compounds under otherwise identical conditions the EPR spectra as shown in Figure 4 were obtained. Simulation of the respective EPR spectra afforded the sets of coupling constants given in Table 3. Irradiation of solutions containing non-labeled (**11**) and labeled PMC acetate (**11***) in the presence of PBN provided two similar EPR spectra (Figure 4C and D). Simulations revealed nearly identical coupling constants (Table 3), clearly showing the absence of an additional coupling constant for the ^{13}C-labeled analogue. Thus, the 5a-position of the acetylated chromanols did not couple with the unpaired electron in the observed spin adducts, and thus the presence of a 5a-carbon centered radical of the acetylated chromanols was safely excluded. The nature of the spin adducts in these experiments was not completely elucidated, but the presence of phenyl adducts from benzene is likely. The slightly different coupling constants compared with those observed by irradiation of PBN in benzene alone might be due to polarity changes, such as the presence of PMC-Ac, cf. Experimental Section. The presence of another trapped radical species cannot be ruled out, even though this species was definitely no 5a-C-radical, which would show the mentioned additional coupling because of the labeling.

In the case of the 6-*O*-acetyl-5a-bromo derivatives of PMC, both labeled (**12***) and in natural isotopic composition (**12**), the 5a-*C*-centered radicals were readily trapped with PBN (Figure 4A and B). The additional coupling in the case of **12*** was an unambiguous proof of the formation of 5a-*C*-centered radicals in that particular case of photochemical generation from suitable benzyl bromide precursors. The value of the additional spin

(42) Rosenau, T.; Habicher, W. D. *Tetrahedron* **1995**, *51*, 7919−7926.

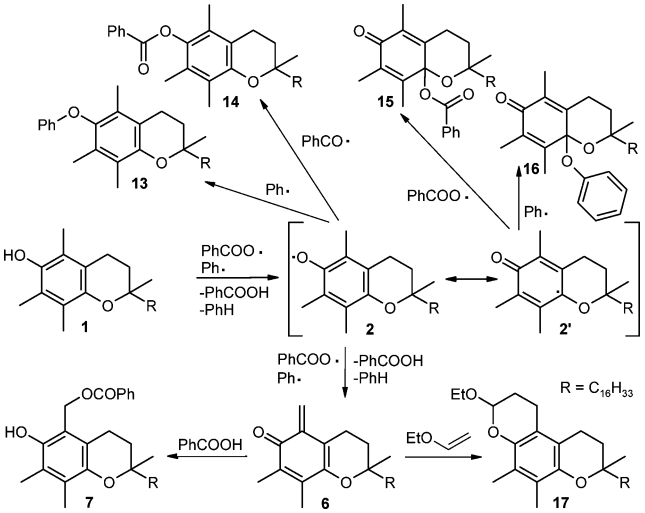
coupling constant of about 3.9 G originating from the ^{13}C nucleus is similar to the additional coupling constant observed with ^{13}C-labeled benzyl bromide (3.6 G); see Scheme 8 and Figure 3. These spectra showed distinctly different splitting patterns for the ^{13}C-labeled compound in comparison to the unlabeled molecule.

In summary, it was demonstrated on the one hand that chromanol-derived 5a-carbon-centered radicals, if formed from suitable precursor compounds, can readily and easily be detected by PBN-trapping in combination with EPR. In our study such radicals were generated by breakage of the photolabile bond in 5a-bromo derivatives. The ease and apparent sensitivity of trapping, on the other hand, allows the reliable conclusion that no such radicals were formed if no corresponding trapping products were found, as in the case of α-tocopherol (**1**), PMC, α-tocopheryl acetate, or PMC acetate (**11**). The experiments thus provided sufficient evidence against the occurrence of α-tocopherol-derived *C*-centered radical species, such as **5**, and against a tautomeric equilibrium between tocopheroxyl radical **2** and benzylic radical **5**.

2.3. Disproving the "Experimental Evidence" for the Occurrence of *C*-Centered Radical 5. The formation of 5a-α-tocopheryl benzoate (**7**) upon reaction of α-tocopherol (**1**) with dibenzoyl peroxide has usually been taken as "solid proof" of the involvement of 5a-*C*-centered radicals in tocopherol chemistry (see Scheme 3). However, there are already some general considerations that render a radical reaction pathway to **7** questionable. First, the yields of 5a-α-tocopheryl benzoate (**7**) can be as high as 30−40%, which seems astonishingly high for a nonselective radical process. Second, it is clear that radicals are involved in the overall process, since dibenzoyl peroxide is a typical radical initiator. It undergoes homolytic cleavage of the O−O bond to form two benzoyloxy radicals that subsequently fragment into CO_2 and phenyl radicals. By reaction of α-tocopherol with these radicals, tocopheroxyl radical **2** with its resonance form **2′** is formed, which undergoes typical radical coupling reactions at positions 6-O and 8a-C (cf. **3** and **4** in Scheme 1, with R′ and R″ being phenyl and benzoyl). Thus, mainly α-tocopheryl phenyl ether (**13**) and α-tocopheryl benzoate (**14**) are formed by reaction of **2** with benzoyl(oxy) and phenyl radicals, respectively. Also, smaller amounts of 8a-benzoyloxytocopherone (**15**) and 8a-phenyloxytocopherone (**16**) were found, originating from recombination of those two radicals with the 8a-*C*-centered resonance form **2′**. Interestingly, for position 5a only benzoate substitution and no phenyl substitution was found. Even if one assumes a slower reaction of the hypothetical tautomeric 5a-*C*-radical **5** with the phenyl radical than with the benzoyloxy radical as in the case of 8a-C, there is no obvious reason why large amounts of benzoyl coupling product but absolutely no 5a-phenyl coupling product was detected.

Starting from such considerations, we were proposing an alternative, heterolytic formation mechanism for **7**, which does not involve 5a-*C*-centered radical species **5**: the initiator-derived radical products generate α-tocopheroxyl radicals (**2**) from α-tocopherol (**1**). The radicals **2** are further oxidized to *o*-quinone methide **6** in a formal H-atom abstraction,[43] thereby converting benzoyloxy radicals to benzoic acid and phenyl radicals to benzene. The generated oQM **6** will add benzoic acid in a [1,4]-addition process, whereas it cannot add benzene in such a fashion. This pathway accounts for the observed occurrence of benzoate **7** and simultaneous absence of a 5a-phenyl derivative and readily explains the observed products without having to involve radical **5**.

SCHEME 10. Major Products of the Reaction of α-Tocopherol (1) with Dibenzoyl Peroxide; Alternative Heterolytic Formation Pathway for 5a-α-Tocopheryl Benzoate (7) without Involvement of 5a-*C*-Centered Radicals and Its Proof by Trapping of *o*-quinone Methide Intermediate 6

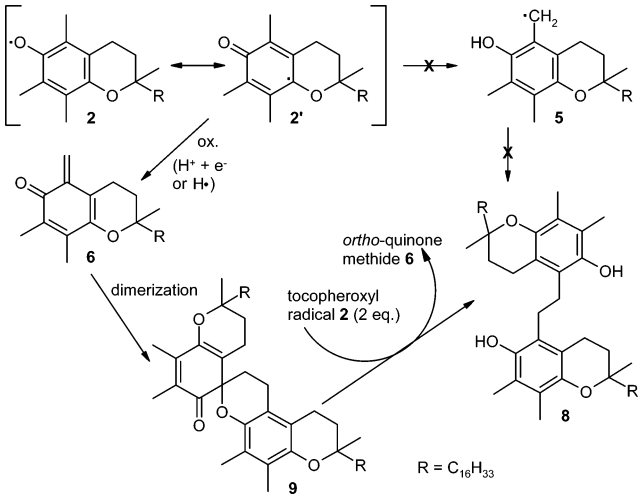


To conclusively disprove the involvement of that species, we conducted the reaction of α-tocopherol with dibenzoyl peroxide in the presence of a large excess of ethyl vinyl ether used as a solvent component. Radical polymerization and recombination reactions of ethyl vinyl ether are disfavored and relatively slow. Therefore, if 5a-α-tocopheryl benzoate (**7**) was formed homolytically according to Scheme 3, the presence of ethyl vinyl ether should have no large influence on the product distribution. However, if **7** was formed heterolytically according to Scheme 10, the intermediate oQM **6** would be readily trapped by ethyl vinyl ether in a hetero-Diels−Alder process with inverse electron demand,[44] thus drastically reducing the amount of **7** formed. Exactly the latter outcome was observed experimentally. In fact, using a 10-fold excess of ethyl vinyl ether relative to α-tocopherol and azobis(isobutyronitrile) (AIBN), no 5a-α-tocopheryl benzoate (**7**) at all was formed but rather the corresponding trapping product **17** was produced, whereas the coupling products of α-tocopheroxyl radical **2**, i.e., compounds **13** and **14** and its 8a-C-resonance structure, i.e., compounds **15** and **16**, were found as in the absence of the trap. Thus, it was shown that the formation of **7** proceeded via oQM **6** without involvement of 5a-*C*-centered radical **5**, and the alleged conclusiveness of the AIBN reaction pro radical **5** was disproved.

(43) In the case of a stepwise process (loss of one electron and one proton), an phenoxonium cation intermediate might well be involved, which has recently been shown to be quite stable: Lee, S. B.; Willis, A. C.; Webster, R. D. *J. Am. Chem. Soc.* **2006**, *128*, 9332−9333. Also the conversion of *p*-quinoid into *o*-quinoid structures in the chemistry of α-tocopherol involves such an intermediate, e.g., the reaction of *p*-tocopheryl quinone with acetyl halide or trimethylsilyl halide to *O*-protected 5a-halotocopherols: (a) Dallacker, F.; Eisbach, R.; Holschbach, M. *Chem. Ztg.* **1991**, *115*, 113−116. (b) Rosenau, T.; Habicher, W. D. *Tetrahedron Lett.* **1997**, *38*, 5959−5960.

(44) This trapping reaction has been frequently applied in vitamin E chemistry, its kinetics and products being well-known; cf. for instance: (a) Rosenau, T.; Potthast, A.; Elder, T.; Lange, T.; Sixta, H.; Kosma, P. *J. Org. Chem.* **2002**, *67*, 3607−3614. (b) Rosenau, T.; Potthast, A.; Elder, T.; Kosma, P. *Org. Lett.* **2002**, *4*, 4285−4288. (c) References 6 and 41.

SCHEME 11. Formation of Ethano-dimer 8 by Reduction of Spiro-dimer 9 in Different Reaction Systems; 5a-*C*-Centered Radicals Are Not Involved in This Process



A second observation, used to support the occurrence of an α-tocopherol-derived 5a-*C*-centered radical, is the formation of α-tocopherol ethano-dimer **8** as the result of radical recombination of two molecules of radical **5** (see Scheme 4). The major components of typical reaction mixtures of α-tocopherol with hydroperoxides in inert solvents are 6-*O*-tocopheryl ethers and 8a-tocopherones (**3** and **4** in Scheme 1), spiro-dimer **9**, ethano-dimer **8**, spiro-trimers,[30] and epoxidized products.[26,28,29,45,46] Typical conditions, which we also used in our experiments, are an equimolar ratio of *tert*-butylhydroperoxide and α-tocopherol in chloroform at room temperature. Under these conditions, ethano-dimer **8** was obtained in 2.4% yield. Already the relatively large amount of ethano-dimer **8** produced (2.4% means that actually 4.8% of the starting α-tocopherol were converted into the dimer) seems to collide with the proposed pathway, since the recombination of two hypothetical 5a-*C*-centered radicals would be expected to be a rather rare event. If the formation of **8** indeed proceeded by radical recombination, then both the increase of competing radicals and high dilution should disfavor the recombination process and decrease the amount of **8** formed. However, repetition of the reaction in the 10-fold amount of solvent did not result in a yield drop: 2.5% of the ethano-dimer was formed. We repeated the reaction with the initial concentrations but with a 10-fold amount of hydroperoxide, which was now used in ratio of 10:1 relative to **1**, and the amount of ethano-dimer even increased from 2.4% to 3.2%. Finally, the reaction was conducted with both a 10-fold amount of solvent and a 10:1 reagent ratio, affording 3.5% of the ethano-dimer. Thus, neither dilution nor the presence of competitive radicals had a depressing effect on the yield of **8**, rendering a radical formation pathway highly unlikely.

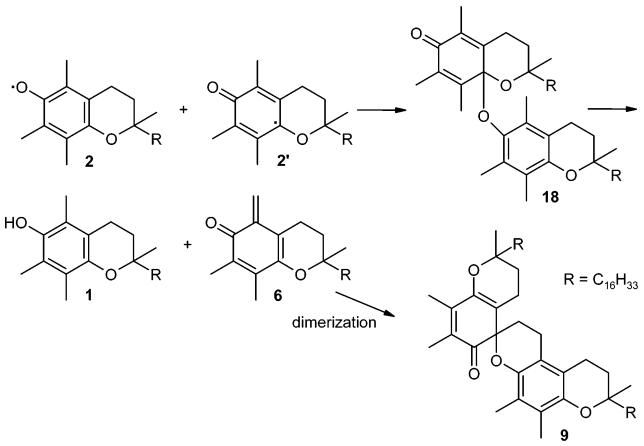
Starting from these results, we proposed an alternative pathway (Scheme 11), according to which the ethano-dimer **8** is formed by reduction of the spiro-dimer **9**. This reduction process is well-known in tocopherol chemistry; ethano-dimer and spiro-dimer have been shown to establish a reversible redox pair. In the present hydroperoxide reaction system, three species, the hydroperoxide, intermediate α-tocopheroxyl radicals, and starting α-tocopherol, could in theory act as the reductant. However, incorporation of the spiro-dimer with *tert*-butylhydroperoxide gave epoxidation products and hydroperoxides, but no ethano-dimer. Also α-tocopherol itself did not reduce the spiro-dimer to the ethano-dimer. However, when we incorporated the spiro-dimer with double molar amounts of AIBN and α-tocopherol, 22% of the ethano-dimer was found, whereas with only AIBN no reduction took place. This demonstrated that the reduction of the spiro-dimer by intermediate tocopheroxyl radicals indeed proceeded. When we used double molar amounts of 2,6-dimethylphenol/AIBN as a source of phenoxyl radicals, as much as 46% of the spiro-dimer was converted into the ethano-dimer, besides polymeric material from dimethylphenol. It should be noted that the yield of ethano-dimer from spiro-dimer could not be increased proportionally with the amount of phenoxyl radicals generated by AIBN/phenol. With increasing overall radical concentrations, side reactions generally become more prominent, and also the ethano-dimer will be increasingly reoxidized to the spiro-dimer. These results unambiguously demonstrated that ethano-dimer **8** in hydroperoxide reaction mixtures of α-tocopherol was not formed by recombination of 5a-*C*-centered radical **5**, but according to a more complex pathway involving the reduction of the spiro-dimer by α-tocopheroxyl or similar phenoxyl radicals (Scheme 11). Thus, also the second alleged proof of the occurrence of **5** in tocopherol chemistry did not hold.

The last reaction commonly evoked to support the involvement of radical species **5** in tocopherol chemistry is the disproportionation of two molecules into the phenol α-tocopherol and the *o*-quinone methide **6** (Scheme 5), the latter immediately dimerizing into spiro-dimer **9**. This dimerization is actually a hetero-Diels−Alder process with inverse electron demand. It is largely favored, which is also reflected by the fact that spiro-dimer **9** is an almost ubiquitous product and byproduct in vitamin E chemistry.[47,48] The disproportionation mechanism was proposed to account for the fact that in reactions of tocopheroxyl radical **2** generated without chemical coreactants, i.e., by irradiation, the spiro-dimer **9** was the only major product found.

As all of our evidence gathered so far disproved the existence of **5**, an alternative pathway (Scheme 12) was proposed, which did not involve the dubious 5a-*C*-centered radical **5** but instead the two well-documented and theoretically sound structures tocopheroxyl **2** and **2′** as its major canonic form. According to general tocopherol chemistry (cf. Scheme 1), **2** and **2′** will recombine in the absence of other coreactants to afford a labile 8a-α-tocopheryl-tocopherone (**18**), which undergoes [1,4]-elimination to afford α-tocopherol (**1**) and *o*-quinone methide **6**, by analogy to other 8a-tocopherones.[49−51] oQM **6**, once formed, will immediately dimerize into **9** in inert media. Thus, this pathway explains the observed product readily on the basis of general tocopherol chemistry without the need to evoke the 5a-*C*-centered radical **5**.

(45) Matsumoto, S.; Matsuo, M.; Iitaka, Y.; Niki, E. *J. Chem. Soc., Chem. Commun.* **1986**, *14*, 1076−1077.
(46) Suarna, C.; Baca, M.; Southwell-Keely, P. T. *Lipids* **1992**, *27*, 447−453.
(47) Schröder, H.; Netscher, T. *Magn. Reson. Chem.* **2001**, *39*, 701−708.
(48) Schudel, P.; Mayer, H.; Metzger, J.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 636−649.
(49) Dürckheimer, W.; Cohen, L. A. *Biochem. Biophys. Res. Commun.* **1962**, *9*, 262−265.
(50) Omura, K. *J. Org. Chem.* **1989**, *54*, 1987−1990.
(51) Kohar, I.; Southwell-Keely, P. T. *Redox Rep.* **2002**, *7*, 251−255.

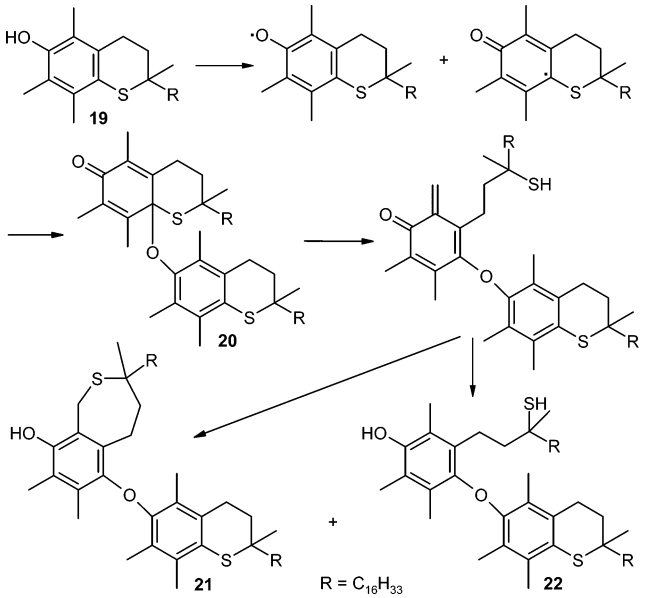
SCHEME 12. Pathway for the Observed Disproportionation of Tocopheroxyl Radical 2 into α-Tocopherol (1) and α-Tocopherol Spiro-dimer (9); 5a-*C*-Centered Radicals Are Not Involved in This Process



Intermediate **18** proved to be rather elusive.[52] In fact an intermediate of similar polarity as compared to **9** was detected by TLC in irradiation mixtures of **1**, but several standard isolation and purification attempts failed. Evidently, the compound was decomposed both on silica gel and on all acid types of alumina upon chromatographic purification. Finally, we used a column of finely powdered potassium carbonate, which upon elution with hexane bound the excess of starting material while letting the tocopherone pass. The reaction had to be performed directly in C_6D_6 as the NMR solvent. $CDCl_3$ as the solvent caused immediate degradation of **18** likely as a result of traces of DCl generated, and so did any attempt of complete solvent removal, even at lower temperatures. The HMBC spectrum of **18** showed characteristic typical long range (^5J) connectivities of the methyl group protons at 2.11 and 2.12 ppm (the 5a and 7a methyl groups in the tocopheryl moiety in **18**, corresponding to ^{13}C resonances at 11.8 and 12.0 ppm) to a carbon at 96.4 ppm (the quinone ketal in the tocopherone part of **18**). Heating of the solution of **18** to temperatures above 50 °C or contact with traces of acids caused immediate formation of α-tocopherol (**1**) and spiro-dimer **9**, confirming the proposed elimination-dimerization mechanism (Scheme 12). Upon degradation of **18**, no 5a-(α-tocopheryl)-α-tocopherol was found, hypothetically formed by [1,4]-addition of α-tocopherol onto *o*-quinone methide **6**, which showed that the dimerization of **6** was by far preferred over that competitive addition path.

A direct proof of the alternative mechanism according to Scheme 12 involved thiotocopherol **19**.[53−56] The compound was selected on the basis of the following consideration: the phenoxyl radical generated from this substance would afford 8a-C-thioketal **20** as the primary radical coupling product (see Scheme 13) by analogy to 8a-tocopherone **18**. In contrast to

SCHEME 13. Disproportionation of Phenoxyl Radicals Derived from Thiotocopherol 19; 5a-*C*-Centered Radicals Are Not Involved in This Process



tocopherone **18**, where the link between the ketal carbon and the aroxy-oxygen is the weakest bond undergoing ready cleavage, the most fragile link in thioketal **20** is the C−S linkage. If intermediate **20** was formed, products of this cleavage should be detectable. Indeed, these products were found: reaction of **19** under otherwise identical irradiation conditions provided 8a-(α-thiotocopheryl)-thiotocopherone **20** by analogy to 8a-(α-tocopheryl)-tocopherone **18** formed from α-tocopherol (**1**). By heating this intermediate to 50 °C or by treatment with acid the thioketal **20** was immediately degraded into a complex product mixture with the main components benzothiepine **21** and bisaryl ether **22**. By irradiation of thiotocopherol **20** at 50 °C benzothiepine **21** (33%) and bisaryl ether **22** (11%) were directly formed along with smaller amounts of oligomers and polymers, at a conversion of 28%. The intermediacy of **18** and **20**, respectively, and the subsequent degradation of those intermediates into the respective products confirmed the mechanism presented in Scheme 12. Thus, the alleged disproportionation proceeds a stepwise process (see Scheme 12) and not just an alteration of oxidation states as the term suggests. It involves as the first step a radical coupling of the *O*-centered radical **2** with its major resonance form **2′** to give 8a-tocopheryl-tocopherone (**18**), which is transformed into the final products by purely heterolytic processes. The net outcome is the observed disproportionation of two tocopheroxyl radicals **2** into phenol **1** (reduction) and a quinoid structure **6** or its dimerization product **9**, respectively (oxidation). 5a-*C*-Centered radical **5** as hypothetic tautomer of α-tocopheroxyl radical **2** is not involved in the whole sequence. Hence, also the third "proof" seemingly supporting the occurrence of radical **5** was shown to be false.

3. Conclusion

In the present paper it has been shown that there is no theoretical evidence for the 5a-*C*-centered radical **5**. In literature accounts, the preference of 5a-C over 7a-C in quinoid structures (often wrongly referred to as the Mills−Nixon effect) has mistakenly been transferred to the case of radical species. However, as the Mills−Nixon effect does not explain the

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behavior of quinoid α-tocopherol-derived structures correctly and was thus replaced by the strain-induced bond localization (SIBL) approach,[6,7] it can, of course, not be used for other α-tocopherol-derived structures. However, even if one accepted the Mills−Nixon theory, it is only applicable to quinoid structures, two-electron oxidation products of α-tocopherol, and cannot be used for radical systems, i.e., one-electron oxidation products. Computations clearly show the favoring of 5a-C in quinoid α-tocopherol-derived systems according to the SIBL concept and equally well disprove any favoring of 5a-C in the α-tocopherol-derived radicals.

The theoretical facts against formation of radical **5** as primary oxidation intermediate of α-tocopherol were complemented by analytical evidence. By combination of EPR spectroscopy with isotopic labeling (^{13}C), it was demonstrated that 5a-*C*-centered radicals were not formed by one-electron oxidation of α-tocopherol or as a tautomer of tocopheroxyl radical **2**. Whereas 5a-*C*-centered radicals were readily generable by alternative pathways, such as photochemical cleavage of 5a-bromo derivatives, and were neatly detected by spin trapping, a similar approach afforded no trapping products at all starting from α-tocopherol. Hence, a tautomeric equilibrium between radical **2** and radical **5** was excluded.

Three reactions are commonly cited to support the occurrence of the chromanol methide radical **5** in vitamin E chemistry: (1) the reaction of α-tocopherol (**1**) with AIBN in inert solvents affording 5a-α-tocopheryl benzoate (**7**) as a major product, (2) the formation of the ethano-dimer (**8**) upon reaction of **1** with hydroperoxides in inert solvents, and (3) the alleged disproportionation of the tocopheroxyl radical **2** with radical **5** leading to regenerated α-tocopherol (**1**) and *o*-quinone methide **6** in the form of its spiro-dimer **9**.

It was shown that all three processes actually follow alternative mechanisms that do not involve radical **5**. For each of those reactions the corrected pathway was proven by trapping methodology, kinetic studies, oxidation of special α-tocopherol derivatives, or combinations of those methods. Thus, finally, all alleged evidence in favor of the formation of the chromanol methide radical **5** from α-tocopherol (**1**) or α-tocopheroxyl (**2**) was refuted.

The questions whether 5a-*C*-centered radicals exist in the oxidation chemistry of α-tocopherol and whether mechanisms proposed in the early days of vitamin E research are correct might appear academic at a first glance, but as soon as one recalls the immense medical, physiological, and economic importance of tocopherol compounds, the significance of an exact knowledge about their basic chemistry becomes obvious, and so this study should be seen as an attempt to advance general understanding in tocopherol chemistry. However, the results of this study have also a direct and immediate impact on two fields of tocopherol research: the synthesis of 5a-substituted derivatives for medicinal or pharmacological applications[57] and the synthesis of polytocopherols as antioxidants, organic magnets, and conductors in material science.[55] For both fields the presence or, more precisely, absence of 5a-*C*-centered radicals derived from α-tocopherol is a key issue, as those species would imply highly undesired effects, such as side reactions with biologically active compounds or cell structures in the first case or cross-linking reactions and chain breakage in the second case. By analogy to the Mills−Nixon theory in tocopherol chemistry having been replaced by the SIBL concept recently, the condoned involvement of 5a-*C*-centered radicals **5** in oxidation reactions of α-tocopherol must be revised. The alternative heterolytic pathways as outlined in this study, shown to afford the observed "radical" products, will have to find their general acceptance in tocopherol chemistry.

4. Experimental Section

4.1. EPR Experiments. Sample Preparation. Solutions of PBN and the respective tocopherols/chromanols were prepared in dry benzene. The solutions were filled into quartz tubes (5.5 mm o.d.) and connected via a valve to a vacuum manifold, which was flushed with argon prior to the experiment. Under light protection, samples were degassed by five consecutive freeze−thaw cycles. Finally, the sample tube including the valve was disconnected from the vacuum manifold and transferred to the EPR spectrometer.

EPR Measurements. Measurements of EPR spectra were performed on a Bruker ESP 300E equipped with a TE_{102} standard cavity. The sealed sample tubes were inserted into the resonator of the EPR spectrometer, and the recording of the spectra was started either immediately after flash illumination (12 W flash energy) or after initiation of continuous irradiation by a mercury HBO 50 lamp. Instrumental settings for measurement of chromanoxyl radicals were as follows: 9.79 GHz; microwave power, 2 mW; receiver gain, 6.3×10^5; modulation frequency, 100 kHz; modulation amplitude, 0.2 G; scan rate, 343 G/min; time constant, 81 ms; temperature, 298 K; scans, 20. For spin trapping experiments: microwave frequency, 9.2 GHz; microwave power, 2 mW; receiver gain, 5×10^5; modulation frequency, 100 kHz; modulation amplitude, 0.25 G; scan rate, 85 G/min; time constant, 81 ms; temperature, 298 K; scans, 10. Control experiments in the solvent benzene revealed that despite a 310 nm cutoff filter used during irradiation a partial photolysis of benzene leading to phenyl radicals and their corresponding spin adducts cannot be avoided. This spin adduct was simulated by the coupling constants $a_N = 14.301 \pm 0.044$ G and $a_{H\beta} = 1.826 \pm 0.029$ G ($n = 3$).

Simulation of EPR Spectra. EPR spectral files from the ESP 300E were imported into the WINSIM program.[34] As starting approximation, data from quantum chemical calculations were used and subsequently fitted to the experimental spectra until at least a regression coefficient of >0.9 was achieved. Always different sets of coupling constants were tested, and the best model was chosen for iterations. The presence of couplings from ^{13}C-labeled atoms was verified by simulation of EPR spectra from unlabeled radicals with a respective dummy coupling constant, which approached a value close to zero.

4.2. Computations. For full geometry optimization the widely employed B3LYP hybrid method was used, as implemented through the GAUSSIAN[58] and SPARTAN[59] program packages, which includes a mixture of HF and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang, and Parr[60,61] parametrized by Becke,[62,63] along with the double-ζ split valence basis

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set 6-31+G*,[64,65] which includes diffuse functions. Transition states and minima were confirmed by analysis of the calculated vibrational spectrum and by intrinsic reaction coordinate analysis. For all transition states the number of imaginary frequencies was 1; for all minimum geometries it was 0.

4.3. Synthesis of 5a-^{13}C-α-Tocopherol (1*-5a). Mannich Reagent. To morpholine (1.05 g, 12.06 mmol) was added portionwise ^{13}C-paraformaldehyde (380 mg, 12.26 mmol, 1.02 equiv), stirring in such a manner that the temperature reached a maximum of 80 °C (exothermic reaction). The reaction was stirred for an additional 3 h at 80 °C, obtaining a colorless solution with a small amount of nonreacted paraformaldehyde. According to ^{1}H NMR data, the solution composition was ^{13}C-morpholinomethanol (A, MW = 117) and ^{13}C-dimorpholinomethane (B, MW = 186) in an 1:1.1 ratio, corresponding to a 34:66 w/w ratio, and minor amounts of polymeric components coming from paraformaldehyde. The solution (referred to as "Mannich reagent" in the following) was used for further manipulations without purification. ^{1}H NMR: δ 2.48 (m, 8 H, NC$\underline{H_2}$CH$_2$ in B), 2.68 (m, 4 H, NC$\underline{H_2}$CH$_2$ in A), 2.87 (d, 2 H, J_{CH} = 138.8 Hz, ^{13}C$\underline{H_2}$ in B), 3.68 (m, 12 H, NCH$_2$C$\underline{H_2}$O in A and B), 4.03 (d, 2 H, J_{CH} = 151.1 Hz, ^{13}C$\underline{H_2}$OH).

5-Morpholino(13C-methyl)-(2*R*,4′*R*,8′*R*)-γ-tocopherol. Mannich reagent (340 mg) was added to (2*R*,4′*R*,8′*R*)-γ-tocopherol (420 mg, 1 mmol), and the resulting mixture was stirred at 80 °C for 4 h. After cooling to room temperature the mixture was diluted with TBME (20 mL) and washed with H_2O until neutral. The organic layer was dried over K_2CO_3. After evaporating the solvent, the residue was purified by column chromatography (hexane/EtOAc, v/v 5:1) affording 5a-^{13}C-5-morpholinomethyl-(2*R*,4′*R*,8′*R*)-γ-tocopherol (480 mg, 93% yield) as dark yellow oil. ^{1}H NMR: δ 0.7−1.9 (m, 38 H, 3-CH$_2$, 2a-CH$_3$ and C$_{16}$H$_{33}$ chain), 2.09 (s, 3 H, 8b-CH$_3$), 2.13 (s, 3 H, 7a-CH$_3$), 2.54−2.61 (m, 6 H, NC$\underline{H_2}$CH$_2$ and 4-CH$_2$), 3.62 (d, 2 H, $^1J_{CH}$ = 134.2 Hz, N-^{13}CH$_2$-Ar), 3.73 (t, 4 H, J = 4.2 Hz, NCH$_2$C$\underline{H_2}$O), 10.6 (s, br, 1 H, O$\underline{H}$). ^{13}C NMR: δ 12.0, 12.1, 19.4, 19.8, 20.7, 21.1, 22.7, 22.8, 23.7, 24.5, 24.8, 28.1, 31.6, 32.7, 32.8, 37.3, 37.4, 37.5, 37.6, 39.4, 39.9, 52.8, 56.7, 66.8, 74.3, 114.4, 116.0, 122.6, 125.2 (d, J_{CC} = 53.12 Hz), 144.4, 148.5.

5a-13C-(2*R*,4′*R*,8′*R*)-α-Tocopherol (1*-5a). To a solution of 5-morpholino(^{13}C-methyl)-(2*R*,4′*R*,8′*R*)-γ-tocopherol (470 mg, 0.91 mmol) in ^{i}BuOH (5 mL) was added NaBH$_3$CN (260 mg, 4.1 mmol, 4.5 equiv), and the resulting mixture was refluxed under stirring for 4 h. Then 3 M HCl was added (8 mL) and the acid aqueous phase was extracted with Et$_2$O (3 × 10 mL). The combined organic phases were washed with NaHCO$_3$ (sat.) and H_2O and dried over Na_2SO_4. After evaporating the solvent, the residue was purified by column chromatography (hexane/EtOAc, v/v 9:1), affording 5a-^{13}C-(2*R*,4′*R*,8′*R*)-α-tocopherol (370 mg, 94% yield) as a yellow oil. ^{1}H NMR: δ 0.7−1.9 (m, 38 H, 3-CH$_2$, 2a-CH$_3$ and C$_{16}$H$_{33}$ chain), 2.15 (s, 3 H, 8b-CH$_3$), 2.19 (s, 3 H, 7a-CH$_3$), 2.14 (d, 2 H, $^1J_{CH}$ = 126.3 Hz, 5a-^{13}CH$_3$), 2.63 (t, J = 6.6 Hz, 2 H, 4-CH$_2$), 4.27 (s, 1 H, OH). ^{13}C NMR: δ 11.2, 11.5, 12.3, 19.7, 19.8, 20.7, 21.0, 22.6, 22.7, 23.8, 24.5, 24.7, 27.9, 31.5, 32.6, 32.7, 37.3, 37.4, 37.5, 37.6, 39.3, 39.7, 74.6, 117.6, 118.8 (d, J_{CC} = 45.08 Hz), 121.1, 122.6, 144.6, 145.6. NMR data are consistent with those from the literature.[56]

4.4. Synthesis of 5a-13C-2,2,5,7,8-Pentamethylchroman-6-ol (PMC*-5a), 6-Acetoxy-5-(bromo-13C-methyl)-2,2,7,8-tetramethylchroman (11*), and 6-Acetoxy-5a-13C-2,2,5,7,8-pentamethylchroman (12*). 5-Morpholino(13C-methyl)-2,2,7,8-tetramethylchroman-6-ol. A mixture of ^{13}C-paraformaldehyde (327 mg, 10.88 mmol) and morpholine (1.81 mL, 13.05 mmol) was heated to 70 °C and a solution of the γ-tocopherol model compound 3,4-dihydro-6-hydroxy-2,2,7,8-tetramethyl-1(2*H*)-benzopyran[66] (1.870 g, 9.06 mmol) in 6 mL of absolute ethanol was added via syringe and heated to reflux for 10 h. After cooling to −4 °C the precipitated product was recrystallized from ethanol to provide 5-morpholino-(^{13}C-methyl)-2,2,7,8-tetramethyl-chroman-6-ol (2.46 g, 89%) as a white solid (mp 135−136 °C). ^{1}H NMR: δ 1.27 (s, 6H, 2a-CH$_3$ and 2b-CH$_3$), 1.76 (t, 2H, 3-CH$_2$, J = 6.8 Hz), 2.10 (3H, s, 7a-CH$_3$), 2.14 (s, 3H, 8b-CH$_3$), 2.56−2.63 (m, 6H, 4-CH$_2$ and N-C$\underline{H_2}$-CH$_2$), 3.64 (d, 2H, ^{13}CH$_2$, $J_{C,H}$ = 134.4 Hz), 3.74 (s, 4H, O-CH$_2$),10.56 (s, br, 1H, OH). ^{13}C NMR: δ 11.7 and 11.9 (7a-CH$_3$ and 8b-CH$_3$), 20.8 (4-CH$_2$), 26.6 (2a-CH$_3$ and 2b-CH$_3$), 33.0 (3-CH$_2$), 52.8 (N-CH$_2$), 56.7 (5a-^{13}C, 99% s, 1% m), 66.7 (O-CH$_2$), 72.3 (2-C), 114.4 (d, 5-C, J_{CC} = 47.5 Hz,), 115.8 (C-4a), 122.7 and 125.2 (C-7 and C-8), 144.5 and 148.5 (C-6 and C-8a).

5a-13C-2,2,5,7,8-Pentamethylchroman-6-ol (PMC*-5a). A solution of 5-morpholino(^{13}C-methyl)-2,2,7,8-tetramethyl-chroman-6-ol (0.597 mmol) in 2-butanol (2 mL) was heated to 70 °C and NaBH$_3$CN (4.776 mmol) was added. The mixture was heated to reflux for 2 h and quenched with 2 M HCl while cooling in an ice bath. The aqueous phase was extracted repeatedly with hexane. The organic layers were combined, washed with saturated NaHCO$_3$ solution and brine, and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by column chromatography (EtOAc/hexane, v/v 1:25) to give 5a-^{13}C-2,2,5,7,8-pentamethylchroman-6-ol **PMC*-5a** (120 mg, 90% yield): mp 93−96 °C. ^{1}H NMR: δ 1.31 (s, 6H, 2a-CH$_3$ and 2b-CH$_3$), 1.81 (t, 2H, 3-CH$_2$, ^3J = 6.9 Hz), 2.14 (d, 2H, 5a-^{13}CH$_3$, $J_{C,H}$ = 126.5 Hz), 2.14 (s, 3H, 7a-CH$_3$), 2.18 (s, 3H, 8b-CH$_3$), 2.64 (t, 2H, 4-CH$_2$, J = 6.9 Hz), 4.21 (s, 1H, OH). ^{13}C NMR: δ 11.2 (5a-^{13}C, 99% s, 1% m), 11.7 (8b-CH$_3$), 12.1 (7a-CH$_3$), 21.0 (4-CH$_2$), 26.7 (2a-CH$_3$ and 2b-CH$_3$), 33.0 (3-CH$_2$), 72.5 (2-C), 117.1 (4a-C), 118.2 (d, J_{CC} = 43.5 Hz, 5-C) 121.1 (7-C), 122.5 (8-C), 144.6 (6-C), 145.7 (8a-C). Anal. Calcd for ^{12}C$_{13}$^{13}CH$_{20}$O$_2$: C, 75.98; H, 9.11. Found: C, 75.93; H, 9.04.

6-Acetoxy-5a-13C-2,2,5,7,8-pentamethylchroman (11*). To a solution of **PMC*-5a** (0.92 g, 4.164 mmol) in dry dichloromethane (30 mL) were added acetic anhydride (2.36 mL, 25.0 mmol) and three drops of concentrated sulfuric acid. The mixture was stirred in a closed flask at room temperature overnight, quenched with saturated NaHCO$_3$ solution, stirred for another 10 min, and extracted with dichloromethane. The combined organic layers were washed two times with brine and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by crystallization from EtOAc/hexane, v/v 1:10, to give **11*** (710 mg, 65% yield): mp 100−102 °C. ^{1}H NMR: δ 1.23 (s, 6H, 2a-CH$_3$ and 2b-CH$_3$), 1.71 (t, 2H, 3-CH$_2$, ^3J = 6.8 Hz), 1.91 (d, 2H, 5a-^{13}CH$_3$, $J_{C,H}$ = 127.2 Hz), 1.95 (s, 3H, 7a-CH$_3$), 2.02 (s, 3H, 8b-CH$_3$), 2.25 (s, 3H, CH$_3$CO), 2.54 (t, 2H, 4-CH$_2$, J = 6.8 Hz). ^{13}C NMR: δ 11.2 (5a-^{13}CH$_3$, 99% s, 1% m). Anal. Calcd for ^{12}C$_{15}$^{13}CH$_{22}$O$_3$: C, 72.97; H, 8.42. Found: C, 73.31; H, 8.49.

6-Acetoxy-5-(bromo-13C-methyl)-2,2,7,8-tetramethyl-chroman (12*). Elemental bromine (147 μL, 2.862 mmol) in dry hexane (60 mL) was added quickly to a solution of **PMC*-5a** (2.806 mmol) in the same solvent (150 mL). The mixture was stirred at room temperature for 1.5 h in a closed flask, and then the formed HBr was removed by evaporation under reduced pressure while the mixture was still stirred. The solvent was removed in vacuo to obtain 5-(bromo-^{13}C-methyl)-2,2,7,8-tetramethylchroman-6-ol quantitatively, which was subsequently dissolved in dry dichloromethane. Acetic anhydride (1.59 mL, 16.836 mmol) and three drops of concentrated sulfuric acid were added, and the mixture was stirred in a closed flask at room temperature overnight. The mixture was quenched with water, stirred for another 10 min, and extracted with hexane/dichloromethane (v/v 1:2). The combined organic layers were washed with saturated NaHCO$_3$ solution and two times with brine and dried over $MgSO_4$, and the solvent was removed in vacuo.

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The crude product was purified by column chromatography (EtOAc/hexane, v/v 1:10) to give 6-acetoxy-5-(bromo-^{13}C-methyl)-2,2,7,8-tetramethylchroman **12*** (750 mg, 78% overall yield): mp 118−121 °C. ^{1}H NMR: δ 1.31 (s, 6H, 2a-CH_3 and 2b-CH_3), 1.83 (t, 2H, 3-CH_2, ^3J = 6.9 Hz), 2.01 (s, 3H, 7a-CH_3), 2.11 (s, 3H, 8b-CH_3), 2.39 (s, 3H, CH_3CO), 2.79 (t, 2H, 4-CH_2, J = 6.9 Hz), 4.39 (d, br, 2H, $^{13}CH_2$Br, $J_{C,H}$ = 151.6 Hz). ^{13}C NMR: δ 25.67 (5a-$^{13}CH_3$, 99% s, 1% m). Anal. Calcd for $^{12}C_{15}{}^{13}CH_{21}BrO_3$: C, 56.15; H, 6.18; Br, 23.34. Found: C, 55.96; H, 6.23.

4.5. Studies into the Reaction of α-Tocopherol with Dibenzoyl Peroxide. Reaction of α-Tocopherol with Dibenzoyl Peroxide. In an Ar atmosphere, a degassed solution of dibenzoyl peroxide (0.870 g, 3.6 mmol) in dry chloroform (30 mL) was quickly added to a degassed solution of α-tocopherol (1.29 g, 3.0 mmol) in the same solvent (15 mL). The mixture was placed into a water bath at 40 °C and stirred for 1 h. The mixture was cooled to room temperature, and the solvent was concentrated in vacuo to a volume of about 3 mL. The yellow, oily residue was chromatographed on neutral alumina (hexane/EtOAc, v/v 5:1) to afford in the order of elution α-tocopheryl phenyl ether (**13**, 18%), α-tocopheryl benzoate (**14**, 22%), 8a-phenyltocopherone (**16**, 8%), 8a-benzoyloxytocopherone (**15**, 4%), and 5a-benzoyloxy-α-tocopherol (**7**, 34%) along with minor byproducts that were not separated. The procedure was repeated three times; the above yields are averaged. An aqueous workup must be avoided as the tocopherones are quite unstable compounds, and compound **7** is degraded in basic media. The analytical data of products **13**−**16** were consistent with previously published data[67] and are therefore not repeated here. The data of **7** are listed for ready comparison.

Benzoic Acid 6-Hydroxy-2,7,8-trimethyl-2-(4,8,12-trimethyl-tridecyl)-chroman-5-ylmethyl ester (5-benzoyloxy-α-tocopherol, 7). ^{1}H NMR: δ 0.72−1.89 (m, 38 H, 3-CH_2, 2a-CH_3 and $C_{16}H_{33}$ chain), 2.10 (s, 3H, 7a-CH_3), 2.15 (s, 3H, 8b-CH_3), 2.60 (t, 2H, ^3J = 6.8 Hz, 4-CH_2), 5.30 (s, 2H, 5a-CH_2), 6.95 (m, 5H, ^{Ar}CH), 10.23 (s, 1H, OH). ^{13}C NMR: δ 11.9 (8b-CH_3), 12.4 (7a-CH_3), 17.9 (4-CH_2), 23.6 (2a-CH_3), 33.6 (3-CH_2), 59.4 (5a-CH_2), 74.2 (2-C), 114.8 (4a-C), 115.5 (5-C), 122.0 (7-C), 123.4 (8-C), 127.1 (4-C in Ph), 129.6 (2-C and 6-C in Ph), 130.6 (1-C in Ph), 132.6 (3-C and 5-C in Ph), 144.6 (6-C), 145.5 (6-C), 166.3 (COO). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found : C, 74.23; H, 7.18.

Reaction of α-Tocopherol with Dibenzoyl Peroxide in the Presence of Trapping Agents. In an Ar atmosphere, a solution of dibenzoyl peroxide (0.870 g, 3.6 mmol) in dry, degassed chloroform (30 mL) was quickly added to a degassed solution of α-tocopherol (1.29 g, 3.0 mmol) in chloroform (10 mL) and ethyl vinyl ether (20 mL). The mixture was placed into a water bath at 40 °C and stirred for 1 h. Every 15 min, 5 mL of ethyl vinyl ether was added. The mixture was cooled to room temperature, and the solvent was concentrated in vacuo to a volume of about 10 mL. The yellow, oily residue was chromatographed on neutral alumina (hexane/EtOAc, v/v 9:1) to afford in the order of elution α-tocopheryl phenyl ether (**13**, 14%), the trapping product of the *o*-quinone methide (**17**, 38%), α-tocopheryl benzoate (**14**, 17%), 8a-phenyltocopherone (**16**, 8%), and 8a-benzoyloxytocopherone (**15**, 6%), along with minor byproducts that were not separated. The procedure was repeated two times; the above yields are averaged. An aqueous workup must be avoided as in the above case. More polar eluant will cause interference with polymerization products of the vinyl ether upon chromatographic separation.

8-Ethoxy-3,5,6-trimethyl-3-(4,8,12-trimethyl-tridecyl)-1,2,3,8,9,-10-hexahydro-pyrano[3,2-f]chromene (17). The NMR and mass spectroscopic data of product **17** were consistent with previously published data.[41,68] Anal. Calcd for $C_{33}H_{56}O_3$: C, 79.14; H, 11.27. Found : C, 79.08; H, 11.34.

4.6. Studies into the Formation of α-Tocopherol Ethano-dimer (8). Reaction of α-Tocopherol with *tert*-Butylhydroperoxide. *tert*-Butylhydroperoxide was used as ∼5.5 M water-free solution in decane as distributed by Sigma-Aldrich. In an Ar atmosphere, a solution of *tert*-butylhydroperoxide in decane (1.8 mL, ∼10 mmol) was added at once to a solution of α-tocopherol (4.30 g, 10.0 mmol) in hexane (50 mL). The mixture was placed into an oil bath at 70 °C and stirred for 5 h. The content of ethano-dimer **8** was determined by HPLC. For preparative separation and purification of this compound, the solution was evaporated to a volume of about 5 mL and chromatographed on basic alumina, eluting the non-phenolic compounds (spiro-dimer **9**, tocopheryl ethers, tocopherones) with (hexane/EtOAc, v/v 9:1). Elution with hexane/EtOAc, v/v 4:1 provided dimer **8** as a yellow oil (210 mg, 2.4%), followed by nonreacted α-tocopherol (8%) and phenolic 5a-substituted α-tocopherols. The reaction was repeated according to the above procedure in 500 mL of hexane, affording **8** (215 mg, 2.5% yield). Using 18 mL of *tert*-butylhydroperoxide solution under otherwise identical conditions (50 mL of hexane), 275 mg (3.2%) of **8** was obtained. With the same amount of hydroperoxide in 500 mL of hexane, the yield of **8** was similar (302 mg, 3.5%).

TABLE 4. Reduction of Spiro-dimer 9 to Ethano-dimer 8 by Different Phenol/Radical Initiator Systems

radical initiator	phenol	yield of **8** [%]
t-BuOOH, 5 mmol	none	0
none	α-tocopherol (**1**), 5 mmol	0
t-BuOOH, 5 mmol	α-tocopherol (**1**), 5 mmol	23
AIBN, 5 mmol	none	0
AIBN, 5 mmol	α-tocopherol (**1**), 5 mmol	22
AIBN, 5 mmol	α-tocopherol (**1**), 10 mmol	28
AIBN, 10 mmol	α-tocopherol (**1**), 5 mmol	16
AIBN, 5 mmol	2,6-dimethyl-phenol, 5 mmol	26
AIBN, 10 mmol	2,6-dimethyl-phenol, 5 mmol	21
AIBN, 10 mmol	2,6-dimethyl-phenol, 10 mmol	46
AIBN, 20 mmol	2,6-dimethyl-phenol, 20 mmol	44

1,2-Bis(5-γ-tocopheryl)-ethane (α-tocopherol ethano-dimer, 8). ^{1}H NMR: δ 0.7−1.9 (m, 38 H, 3-CH_2, 2a-CH_3 and $C_{16}H_{33}$ chain), 2.12 (s, 4 × 3H, 7a-CH_3 and 8b-CH_3), 2.65 (t, 4H, ^3J = 6.7 Hz, 4-CH_2), 3.70−4.30 (s, br, 2H, OH). ^{13}C NMR: δ 12.2 (8b-CH_3), 12.4 (7a-CH_3), 20.6 (4-CH_2), 23.7 (2a-CH_3), 24.8 (5a-CH_2), 33.8 (3-CH_2), 75.5 (2-C) 117.1 (4a-C), 121.5 (5-C), 121.7 (7-C), 122.8 (8-C), 144.6 (6-C), 145.8 (8a-C). Anal. Calcd for $C_{58}H_{98}O_4$ (859.42): C, 81.06; H, 11.49. Found: C, 81.15; H, 11.44.

An authentic sample of **8** was prepared by refluxing 5a-bromo-α-tocopherol with the 8-fold molar amount of $Fe(CO)_9$ in hexane for 1 h. Yields were quantitative, requiring no chromatographic purification. Anal. Calcd for $C_{58}H_{98}O_4$ (859.42): C, 81.06; H, 11.49. Found: C, 81.12; H, 11.53.

Reduction of Spiro-dimer 9 by Intermediate Phenoxyl Radicals to Ethano-dimer 8. To a solution of α-tocopherol spiro-dimer **9** (0.20 g 0.23 mmol) in hexane were quickly added a solution of a radical initiator (10 mL of hexane, 0.5 mmol) and the solution of a phenol in the same solvent (10 mL pro 0.5 mmol). The mixture was placed into an oil bath at 70 °C and stirred for 1 h. The content of ethano-dimer **8** was determined by HPLC. The types and amounts of initiator and phenols used together with the yields of ethano-dimer **8** obtained are given in Table 4.

4.7. Studies into the Disproportionation of Tocopheroxyl Radicals. Irradiation of α-Tocopherol in Inert Solvents. A solution of α-tocopherol (2.15 g, 5 mmol) in dry, perdeuterated benzene (50 mL) was irradiated for 10 h by a mercury HBO 200 W lamp under external cooling at 10 °C. At this temperature, the mixture was concentrated to a volume of 5 mL and chromatographed at room temperature on powdered anhydrous K_2CO_3 using C_6D_6 as the eluant. After minor amounts of tocopheryl phenyl ether and other non-identified non-pehnolic byproducts, 8a-α-tocopheryl-tocopherone (**18**) was eluted. The fraction containing **18** was concentrated at 0 °C to about 0.5 mL and directly measured by

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NMR. The amount of **18** formed (32 mg, 1.4%) was calculated from the amount of **1** and **9** formed by acid treatment.

Preparation of Thiotocopherol 19. Thiotocopherol **19** was prepared according to the literature[51,53] in satisfactory purity. The NMR data agreed with one literature report[53] but showed some small deviations from another one.[54]

Irradiation of Thiotocopherol 19 in Inert Solvents at 10 °C. Irradiation of thiotocopherol **19** and purification of the reaction intermediate **20** (38 mg, 1.7%) was performed according to the above procedure.

Irradiation of Thiotocopherol 19 at 70 °C. Working according to the above irradiation procedure but at 50 °C afforded **21** and **22** as degradation products of **20** directly. Also thermal treatment of **20** at 80 °C for 1 min or treatment with 1 drop of TFA at room temperature provided a compound mixture with **21** and **22** as the main components. A solution of thiotocopherol **19** (2.23 g, 5 mmol) in dry cyclohexane (50 mL) was irradiated for 10 h by a mercury HBO 200 W lamp at 50 °C. The greenish mixture was concentrated to a volume of 5 mL and chromatographed on basic alumina using an hexane/EtOAc eluant (v/v 5:1) deacidified by filtration over K_2CO_3 shortly before use. After two minor non-identified byproducts and nonreacted starting material, benzothiepin **21** eluted as a yellow oil. Changing the eluant to hexane/EtOAc eluant (v/v 3:1) afforded the thiol **22** as colorless waxy solid. The reaction was repeated three times with the retrieved starting material of the previous run. At 28% conversion of thiotocopherol **19**, yields of benzothiepin **21** and thiol **22** were 209 mg (33%) and 72 mg (11%), respectively.

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Supporting Information Available: Preparation and NMR data (^{1}H, ^{13}C) of 7-morpholino(^{13}C-methyl)-(2*R*,4′*R*,8′*R*)-*β*-tocopherol and 7a-^{13}C-(2*R*,4′*R*,8′*R*)-α-tocopherol (**1*-7a**). NMR (^{1}H, ^{13}C) and purity data of 8a-α-tocopheryl-tocopherone (**18**), 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-thiochroman-6-ol (**19**), 8a-α-thiotocopheryl-thiotocopherone (**20**), 3,7,8-trimethyl-6-[2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-thiochroman-6-yloxy]-3-(4,8,12-trimethyltridecyl)-1,3,4,5-tetrahydrobenzo[*c*]thiepin-9-ol (**21**), and 3-(3-mercapto-3,7,11,15-tetramethylhexadecyl)-2,5,6-trimethyl-4-[2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-thiochroman-6-yloxy]-phenol (**22**). Computational details for radicals **2**, **5**, and **5a** as well as *o*-quinone methides **6** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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