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Synthesis of the Phenoxonium Cation of an α-Tocopherol Model Compound Crystallized with Non-Nucleophilic $[B(C_6F_5)_4]^-$ and $(CB_{11}H_6Br_6)^-$ Anions

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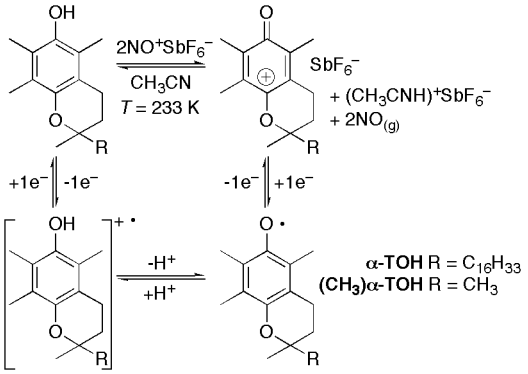
We report the crystal structure of a phenoxonium cation of a vitamin E model compound whose high stability is directly attributable to the chromanol structure and the degree of methylation around the phenolic aromatic ring. The crystallographic data are in excellent agreement with structural results from molecular orbital calculations.

Vitamin E's role solely as an antioxidant[1] in biological systems has become increasingly difficult to justify in recent years in light of the discovery of a number of new functions.[2] α-Tocopherol (α-TOH), the fully methylated form of vitamin E, has been found to display specific nonantioxidant functions, such as the inhibition of protein kinase C (PKC), that are not shared by the less methylated tocopherols (*β*-, *γ*- and *δ*-).[3] The α-tocopherol transfer protein (α-TTP)[4] is responsible for regulating α-TOH plasma levels and preferentially binds the tocopherols in the order $\alpha > \beta > \gamma \gg \delta$,[5] but it is not clear why α-TOH is chemically preferred to the other tocopherols. There must be some mechanistic property possessed by α-TOH that causes it to interact in a special way with PKC, which is missing from the other tocopherols. Chemical differences between the tocopherols have focused on differences in rate constants associated with their antioxidant function,[1] but it has been demonstrated that the electrochemical properties of the tocopherols also differ.[6,7] In particular, α-TOH has been shown to form a stable (for a few hours) phenoxonium cation (α-TO^+) upon oxidation in dry organic solvents at low temperatures, where the other oxidized tocopherols are considerably less stable.[7d]

The electrochemical behavior of α-TOH and the model compound where the phytyl chain is replaced with a methyl group, (CH_3)α-TOH, have been shown to be identical.[7c,7d] Therefore, experiments aimed at isolating the phenoxonium cation were performed with (CH_3)α-TOH, because it was believed to be more likely obtained as a solid than the oil-like natural compound and because (CH_3)α-TO^+ was known to be even more stable than α-TO^+ in solution.[8] The oxidation reaction encompassing the formation of the phenoxonium cation occurs via two one-electron steps interposed with the loss of a phenolic proton (Scheme 1), previously established by detailed electrochemical and spectroscopic experiments (an electrochemical ECE mechanism).[7b−7d] The reaction in Scheme 1 produces the phenoxonium cation in 100% yield in solution and can be controlled either electrochemically or chemically using NO^+ as the oxidizing agent.[9] The byproducts of the chemical oxidation reaction are 1 equiv of acid (represented in Scheme 1 as coordinated to the solvent) and 2 equiv of NO gas.

$NOSbF_6$ (2.4 mmol) was added to a solution of 1.2 mmol (CH_3)α-TOH in 2 mL of CH_3CN at 233 K and mixed for 1 h. $Cs(CB_{11}H_6Br_6)$[10] or $K[B(C_6F_5)_4]$[11] (1.2 mmol) was added to the CH_3CN, and the solvent was removed with a diffusion pump ($p = 10^{-5}$ mmHg). The orange solid was warmed to 253 K and dissolved in 5 mL dichloroethane and filtered under nitrogen to remove insoluble material. A 0.5 mL aliquot of the solution was further diluted with 10 mL of dichloroethane, and the solution was left at

Scheme 1. Mechanism for the Formation of Phenoxonium Cation



253 K for 2 weeks in a N_2 environment, during which time a few orange crystals formed. The crystals were unstable in air, but when coated in Paratone oil could be stabilized sufficiently to enable mounting on an X-ray diffractometer, with the crystals subsequently maintained in a stream of N_2 gas at 200 K while the data were collected.

Because of instability in the presence of moisture and decreasing stability at ambient temperatures in solution, (CH_3)α-TO^+ has proven difficult to separate from the acid as the SbF_6^- or PF_6^- salts, and crystals did not form directly in the presence of those anions. The $[B(C_6F_5)_4]^-$ and $(CB_{11}H_6Br_6)^-$ anions have been reported to be extremely non-nucleophilic and have been used to stabilize a number of organic and inorganic cations,[12] and in this instance, their solubility properties facilitated crystallization of the phenoxonium cation. The choice of NO^+ as the oxidizing agent for the reaction in Scheme 1 is very important; using Ag_2O or Br_2 results in the formation of a reactive intermediate quinone methide (via a two electron, two proton process), which quickly reacts further.[13]

Higher precision X-ray data were obtained for the (CH_3)α-TO^+ cation when crystallized with the $[B(C_6F_5)]^-$ anion than with the bromo−carborane anion. The C_4-O_1, C_2-C_3, and C_5-C_6 bond lengths in (CH_3)α-TO^+ are typical of compounds with a quinone structure (Figure 1 and Table 1), which agree with solution phase infrared studies that detected strong absorbancies at 1670, 1649, and 1605 cm^{-1} due to a C═O stretch and symmetric and asymmetric C═C ring stretches, respectively.[7b−7d] The C_1-O_2 bond length in (CH_3)α-TO^+ is significantly shorter than in the parent phenol and is between what is expected for a single and double bond. The C_9-O_2 bond length in the phenoxonium cation (1.520 Å) is much longer than expected for a C−O single bond (1.44 Å). The increased C_9-O_2 bond length in the phenoxonium cation correlates with ^{13}C NMR data and molecular orbital calculations that indicated increased positive charge on C_9 (and C_1).[7c]

The high stability of the phenoxonium cation can be rationalized by the chromanol ring maintaining structural integrity around C_9 despite the long and, therefore, weak C_9-O_2 bond. The C_6-C_7-

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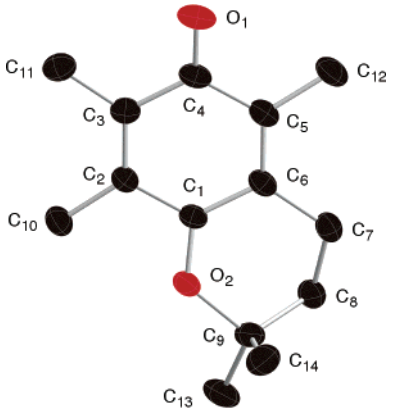

Figure 1. ORTEP plot for the molecular structure of $(CH_3)\alpha$-TO^+ (crystallized with the $[B(C_6F_5)_4]^-$ counteranion). Thermal ellipsoids are drawn at the 50% probability level and hydrogen atoms are omitted.

Table 1. Selection of Crystallographic Bond Lengths[a]

	Bond Length/Å		
		$(CH_3)\alpha$-TO^+	
	$(CH_3)\alpha$-TOH[b]	$[B(C_6F_5)_4]^-$	$(CB_{11}H_6Br_6)^-$
bond	$R(F) = 0.0382$	$R(F) = 0.0316$	$R(F) = 0.0321$
C_1-O_2	1.3827(12)*1.374*	1.282(3) *1.289*	1.296(5)
C_4-O_1	1.3950(13)*1.377*	1.214(3) *1.217*	1.219(6)
C_1-C_2	1.4055(14)*1.404*	1.455(4) *1.454*	1.468(7)
C_3-C_4	1.3974(15)*1.399*	1.488(4) *1.498*	1.511(7)
C_2-C_3	1.3954(14)*1.398*	1.355(4) *1.360*	1.324(7)
C_5-C_6	1.4012(15)*1.406*	1.355(4) *1.359*	1.339(7)
C_9-C_8	1.5217(16)*1.526*	1.515(4) *1.519*	1.503(7)
C_9-C_{13}	1.5159(16)*1.521*	1.518(5) *1.516*	1.516(8)
C_9-C_{14}	1.5207(16)*1.529*	1.511(5) *1.521*	1.515(7)
C_9-O_2	1.4566(12)*1.440*	1.520(4) *1.510*	1.534(6)

[a] Results from theoretical (EDF2/6-31+G*) calculations are in italics.[7c] [b] Values are given for one of the two molecules in the crystallographic asymmetric unit.

C_8-C_9 bond lengths and bond angles remain very similar in going from $(CH_3)\alpha$-TOH to $(CH_3)\alpha$-TO^+. The C_1-C_2 and C_1-C_6 bonds in the conjugated $(CH_3)\alpha$-TO^+ are shorter than the C_4-C_3 and C_4-C_5 bonds, due to relatively more positive charge located on C_3 and C_5 compared to C_2 and C_6. The bond lengths are all within 0.01 Å and the bond angles are all within 1° (for the $[B(C_6F_5)_4]^-$ complex) of the results obtained from molecular orbital calculations.[7c] The exceedingly high agreement between experiment and theory in the structure of the neutral and charged tocopherols is due to the high level of accuracy of the EDF2/6-31+G* model (Table 1)[14] and because the nonnucleophilic anions do not interact strongly enough to distort the structure of the cation beyond theoretical predictions.

In theory, all phenols should undergo the reaction in Scheme 1,[15] although vitamin E is unusual in the high stability of the phenoxonium cation (of α-TO^+) and the high persistence of the intermediate cation radicals (of all the tocopherols), which are stable in the presence of organic-soluble acids.[7d] There are few other reports of phenols that form stable phenoxonium ions upon oxidation; 2,6-di-*tert*-butyl-4-(4-dimethylaminophenyl)-phenol, which has bulky substituents in the 2- and 6-positions and an electron donating group in the 4-position,[16] and a metal stabilized phenoxonium complex.[17]

The proposed high importance of α-TOH compared to the other tocopherols in terms of antioxidant properties has been based on a <10-fold difference in the rate of a hydrogen atom abstraction reaction spanning all the tocopherols in organic solvents (the difference in rate is <2-fold between α-TOH and β-TOH).[1a] This compares to *at least* a 10^4 difference in stability (in solution) between α-TO^+ and δ-TO^+,[7d] possibly much longer in light of the demonstrated ability to crystallize $(CH_3)\alpha$-TO^+.

It has been argued that the chromanol structure is crucial to vitamin E's role as an antioxidant by imparting a favorable geometry on the ether oxygen with respect to the aromatic plane, increasing the p-orbital overlap and thereby improving the stability of the α-$TO^\bullet$ radical.[1a] This work has demonstrated that the chromanol structure (and phenolic methyl groups) also impart stability on the phenoxonium cation. The implication of the high stability of α-TO^+ is that it is also critical in vitamin E's true biological function(s), especially considering that phenoxonium cations are usually unstable.[15]

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Supporting Information Available: Crystallographic data and theoretical bond lengths and angles from molecular orbital calculations (54 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) ^{13}C NMR experiments indicated that $(CH_3)\alpha$-TO^+ was stable for at least 24 h at 233 K in CD_3CN, whereas α-TO^+ showed evidence of decomposition/reactivity after ~2 h.[7b,7c]
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