

Table VII. Parameters Required for Calculation of Resonance Integrals

Bond	D'' , eV	D' , eV	r'' , Å	r' , Å	a'' , Å ⁻¹	a' , Å ⁻¹	F , Å	G , Å
CC	5.5600	3.9409	1.338	1.512	2.3177	2.0022	1.512	0.174
CO	7.1011	3.9559 (3.9987)	1.208 (1.230)	1.395	2.1787	1.7190 (1.7870)	1.395	0.187 (0.165)

parallel those of the corresponding hydrocarbons. Figure 2 shows the correlation obtained. A fair correlation coefficient of 0.920 was found. The average deviation of points was 0.05 V. As a single correlation this is appreciably better than has been evaluated to date.

Acknowledgments. We thank the Oregon State University Computer Center for providing the funds for these calculations.

Appendix

As has been stated in the text, the standard Dewar-Morita parameterization for calculation of resonance integrals and their variation as a function of bond length was modified for carbon-oxygen bonds. This was

necessitated by the use of a shorter value for an unconjugated carbon-oxygen double bond. Using standard notation, Table VII contains the values of bond energies (D), equilibrium bond lengths (r), Morse constants (a), and empirical parameters F and G required in a Dewar-Schmeising thermocycle. The superscripts refer to unconjugated double bonds and "pure" sp^2-sp^2 single bonds. The final two terms in the table are utilized to calculate bond length as a function of bond order by the equation

$$r = F - Gp$$

Those entries in parentheses are those originally used by Dewar and Morita. No other changes in parameterization were made. All one center terms may be found in Table I of ref 17.

Electrochemistry in Media of Intermediate Acidity.

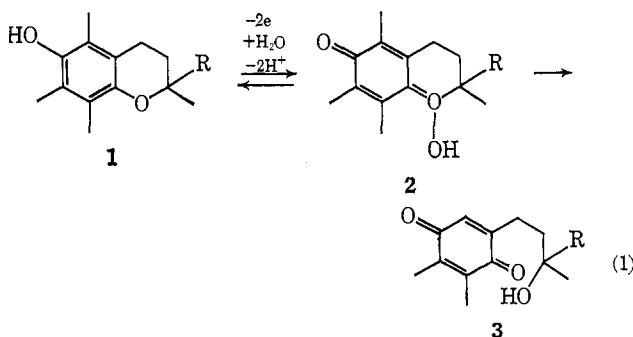
VIII. Reversible Oxidation Products of the α -Tocopherol Model Compound. Cation Radical, Cation, and Dication¹

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Abstract: In acetonitrile, the α -tocopherol model compound (**1**) undergoes "reversible" two-electron oxidation, the degree of reversibility depending upon the proton concentration. In the presence of strong acid, the two-electron oxidation product is stable and spectral measurements indicate that it has the dication structure **7**. Oxidation of **1** in trifluoroacetic acid or in dichloromethane-trifluoroacetic acid results in the reversible formation of the cation radical **9**. The acidity of **9** is unusually low as compared to other phenolic cations. The dication **7** can be generated by chemical oxidation of solutions of **9** by addition of chemical oxidants such as perchloric acid. Likewise, **7** can be generated directly by the action of antimony pentachloride in dichloromethane solution. The two-electron oxidation product in acetonitrile containing acid is the phenoxonium ion, **8**, which is remarkably stable in that medium.

The widespread occurrence of α -tocopherol and related chromanols in nature² and their action as natural antioxidants have prompted a host of chemical studies on their redox behavior. Many investigators have attempted to find the copartner of α -tocopherol in the reversible oxidation-reduction couple detected polarographically.³ Smith and coworkers, who worked with 50% aqueous methanol solutions, suggested that the reversible couple was **1** - $2e \rightleftharpoons$ **2** and that **2** was unstable reacting irreversibly to form **3**.³ Boyer later



(1) Part VII: O. Hammerich and V. D. Parker, *J. Amer. Chem. Soc.*, in press.

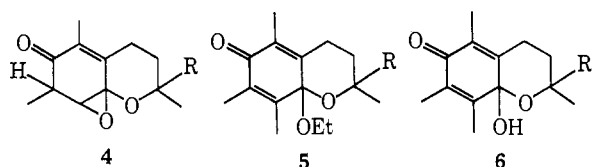
(2) R. A. Morton, "Biochemistry of Quinones," Academic Press, New York, N. Y., 1965.

(3) L. I. Smith, I. M. Koltoff, S. Wawzonek, and R. M. Ruoff, *J. Amer. Chem. Soc.*, **63**, 1018 (1941).

believed that he had isolated the two-electron oxidation product and assigned the epoxide structure, **4**.⁴ It was

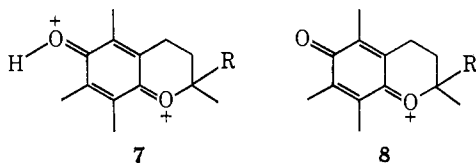
(4) P. D. Boyer, *J. Amer. Chem. Soc.*, **73**, 733 (1951).

later shown that " α -tocopheroxide" was not polarographically reducible forcing the conclusion that it could not be the reversible oxidation product.⁵ The oxide structure was later shown to be incorrect, the compound actually being 9-ethoxy- α -tocopherone (5).⁶ Dürckheimer and Cohen succeeded in preparing 9-hydroxy- α -tocopherone (6)⁷ which has found wide ac-



ceptance as the partner of α -tocopherol in the reversible oxidation reduction couple.⁸

Recent studies employing electroanalytical techniques have supported the earlier electrochemical study³ showing that the α -tocopherol model compound (1) undergoes a reversible oxidation in acetonitrile to give an intermediate with a measurable lifetime.⁹⁻¹¹ Two different proposals were put forth for the nature of the initial two-electron oxidation product: the first being that it has the dication structure (7)⁹ and the other that it is a deprotonated form (8).^{10,11}



In this paper we examine the effect of going to more acidic solvents for the oxidation of 1 and present spectral evidence for the nature of the initial oxidation products.

Results

Oxidation of the α -Tocopherol Model Compound (1) in Media Containing Trifluoroacetic Acid (TFA). Cyclic voltammetry of 1 in dichloromethane-TFA (3:1) containing $n\text{-Bu}_4\text{NBF}_4$ (0.2 M) showed that 1 is oxidized at +0.80 V.^{12a} The cathodic segment of the voltammogram showed a reduction peak at +0.74 V and the ratio of cathodic to anodic currents was equal to 1.0 indicating that the oxidation of 1 is a reversible one-electron process which produces an intermediate, stable under the conditions of slow sweep cyclic voltammetry. Nearly identical behavior was observed in pure TFA. Constant current coulometry^{12b} in either of the solvent systems resulted in the consumption of 1.0 faraday/mol and the formation of a relatively stable one-electron oxidation product, with structure 9 or 10 which is nearly indistinguishable by electrochemical techniques in acidic media. However, the phenoxy

(5) W. H. Harrison, J. E. Gander, E. R. Boyer, and P. D. Boyer, *Biochim. Biophys. Acta*, **21**, 150 (1956).

(6) C. Martius and H. Ellingsfeld, *Justus Liebigs Ann. Chem.*, **607**, 159 (1957).

(7) W. Dürckheimer and L. A. Cohen, *J. Amer. Chem. Soc.*, **86**, 4388 (1964).

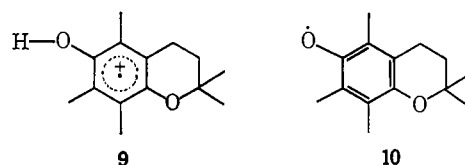
(8) J. Green and D. McHale in "Biochemistry of Quinones," R. A. Morton, Ed., Academic Press, London, 1965, p 268.

(9) V. D. Parker, *J. Amer. Chem. Soc.*, **91**, 5380 (1969).

(10) M. F. Marcus and M. D. Hawley, *Biochem. Biophys. Acta*, **201**, 1 (1970).

(11) M. F. Marcus and M. D. Hawley, *J. Org. Chem.*, **35**, 2185 (1970).

(12) (a) All potentials refer to oxidation or reduction at a platinum electrode vs. the saturated aqueous calomel electrode; (b) V. D. Parker, *Acta Chem. Scand.*, **24**, 2768 (1970).



radical (10) would be expected to undergo further oxidation to give the cation (8) at a lower potential than required to oxidize 1.¹³ In TFA or in dichloromethane-TFA (3:1) it was not possible to see a clearly defined oxidation peak for the oxidation of the one-electron intermediate. However, when TFA anhydride was added to a solution of the one-electron oxidation product in dichloromethane-TFA (3:1), the background was diminished sufficiently so that a clearly defined oxidation peak was observed at +1.34 V, *i.e.*, at a potential 640 mV more anodic than necessary to oxidize 1.

Stability and Structure of the One-Electron Oxidation Product. The visible absorption spectrum of the yellow green solution of the oxidation product of 1 in TFA showed a maximum at 456 nm (ϵ 610). Only a 10% decrease in the absorption at 456 nm was observed after allowing the TFA solution to stand at room temperature for 6 hr. A similar solution diluted 1:1 with concentrated sulfuric acid showed approximately the same stability.

Esr Spectra of the One-Electron Oxidation Product. In order to verify the structure of the one-electron oxidation product, the esr spectra in media of varying composition were examined. The spectra clearly confirm that the product is 9 rather than 10. The esr spectra of 9 were nearly identical in the following low viscous media of varying acidity: H_2SO_4 -TFA (1:1), dichloromethane-methanesulfonic acid (5:2), TFA, and dichloromethane-TFA (3:1). The room-temperature spectrum in the latter medium is shown in Figure 1a. The spectrum is complex exhibiting at least 20 resolved lines, some of which are further split. The dramatic change which takes place upon either cooling the dichloromethane-methanesulfonic acid solution to -60° or by recording the spectrum of a concentrated H_2SO_4 solution at $+5^\circ$ is illustrated in Figure 1b. The latter spectrum consists of at least six separate groups of lines. The spectrum of 9 in TFA- d - D_2SO_4 or TFA- d at room temperature is shown in Figure 1c.

The fact that the spectra exemplified by Figure 1a are identical in the various media shows that the same species exists in every case. The spectral changes obtained by cooling (Figure 1b) or going to more viscous media are due to the existence of *cis-trans* isomers by virtue of slow rotation of the hydroxylic group. Similar spectral changes have been observed during examination of the durohydroquinone cation radical in strongly acid media.¹⁴ The spectral changes observed in going from Figure 1a to Figure 1c are due to rapid exchange of the hydroxylic hydrogen with deuterium.

Oxidation of 1 in Acidic Acetonitrile. The cyclic voltammogram of 1 in MeCN-TFA (9:1) consisted of a quasi reversible two-electron redox couple with the potentials of both the oxidation and reduction peaks

(13) Phenoxy radicals in general are believed to oxidize more readily than the parent phenols; for example, the 2,4,6-tri-*tert*-butylphenoxy radical has been observed to oxidize about 300 mV more readily than the corresponding phenol: A. B. Suttie, *Tetrahedron Lett.*, 953 (1969).

(14) J. R. Bolton and A. Carrington, *Mol. Phys.*, **5**, 161 (1962).

Table I. Sweep Rate Dependence of the Redox Potentials of **1** in MeCN-TFA (9:1)

	Sweep rate ^a						
	15.6	(30.9)	(61.8)	(124)	15	(236)	(300)
E_o^b	810	815	820	830	830	830	835
E_r^c	710	700	685	670	670	650	655
ΔE^d	100	115	135	160	160	170	180

^a mV/sec. ^b Oxidation peak potential in mV. ^c Reduction peak potential in mV. ^d Difference in peak potentials in mV.

being dependent upon the voltage sweep rate (Table I). Constant current coulometry of **1** in MeCN-TFA (9:1) containing NaClO₄ (0.1 M) resulted in the consumption of 2.0 faradays/mol and produced a solution of the 2e oxidation product. Voltammetry of the resulting solution showed the same redox couple as was observed before oxidation indicating that the primary oxidation product is stable in the medium. Coulometric reduction regenerated **1** and indicated that less than 20% loss of substrate had occurred during the oxidation reduction cycle which required about 20 min. The visible spectrum of the oxidation product taken immediately after generation consisted of a single broad maximum at 460 nm (ϵ_{obsd} 790). The decrease in intensity of the maximum with time was used to estimate the half-life of the intermediate as being of the order of 30 min. When a MeCN-TFA (9:1) solution of **3** was acidified with a drop of concentrated H₂SO₄ the quinone (**3**) was converted rapidly to the cation (**8**).¹⁵ The visible absorption spectrum showed the broad maximum at 460 nm (ϵ_{obsd} 950) immediately after mixing, and the half-life of the cation under these conditions was of the order of 10 min. It is difficult to estimate the true extinction coefficient of the cation but it must be somewhat greater than 1000.

The peak separation during cyclic voltammetry of **1** in acetonitrile was found to be very dependent upon the acidity. At a voltage sweep rate of 15.6 mV/sec, the following values of ΔE were observed: in MeCN, 110 mV; in MeCN-TFA (9:1), 100 mV; in MeCN-MeSO₃H (25:1), 62 mV; in MeCN-H₂SO₄ (100:1), 60 mV; in MeCN-H₂SO₄ (20:1), 50 mV; and in MeCN-H₂SO₄ (10:1), 42.5 mV. Thus, as the acidity of the medium is increased the oxidation of **1** approaches reversibility as a direct two-electron transfer.

Oxidation of 1 with Antimony Pentachloride in Dichloromethane. Upon mixing in a solution of SbCl₅-dichloromethane (1:10), **1** is converted to an ion, the visible absorption spectrum of which shows a broad band with a maximum at 465 nm (ϵ 1440). The solution showed no sign of decomposition even upon standing at room temperature for 5 days. While similar in shape to the band assigned to the monocation (**8**), the band in this case was considerably broader. For example, the ratio of absorbance at the maximum to that at 500 and 550 nm was as follows: $A_{\text{max}}/A_{500} = 1.3$ for the SbCl₅ oxidation product and 1.8 for the monocation (**8**), while $A_{\text{max}}/A_{550} = 3.8$ for the former and 7.9 for the latter ion.

Structure of the SbCl₅ Oxidation Product. Nmr

(15) The structure of the oxidation product and that from cyclization of **3** was assigned the monocation (**8**) rather than the dication structure (**7**) because of the observation of a different spectrum for the dication in more acidic media.

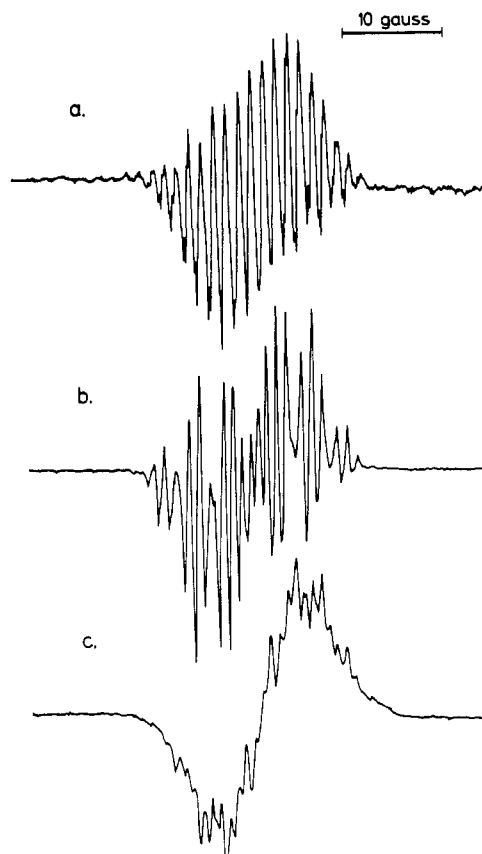
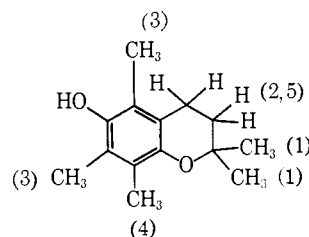


Figure 1. Esr spectra of **9** in varying media: (a) **9** in CH₂Cl₂-TFA (3:1) at room temperature; (b) **9** in CH₂Cl₂-CH₃SO₃H (5:2) at -60°; (c) **9-d** at room temperature.

Table II. Nmr Spectral Data for the α -Tocopherol Model Compound and the SbCl₅ Oxidation Product



	Protons				
	(1)	(2)	(3)	(4)	(5)
Substrate (1)	8.73 s	7.4 t	7.4 s	7.90 s	8.23 t
Dication (7)	8.22 s	7.12 t	7.76 s	7.71 s	7.69 t
			7.77 s		
			7.86 s		
			7.87 s		

spectral data for **1** in CDCl₃ and for the SbCl₅ oxidation product in CD₂Cl₂ are summarized in Table II. All proton signals are shifted toward lower field in the oxidation product. The most significant differences in the substrate and oxidation product spectra are found in the signals due to the two methyl groups adjacent to the hydroxyl function. In the spectrum of **1**, a single signal due to all six protons is observed at τ 7.4 while a pair of doublets is observed in the spectrum of the oxidation product. The splitting is strong evidence that the oxidation product has the dication structure (**7**) with the proton unsymmetrically placed on the oxygen.

Thus, the splitting is due to the two different conformers around the OH function.¹⁶

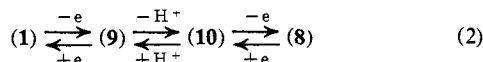
The inversion of the oxygen containing ring is fast at room temperature on the nmr time scale since only a sharp singlet is observed for the two methyl groups (1). A broadening is observed on lowering the temperature: however, no splitting was observed even at -60° which was the lower limit due to insolubility of the dication. Therefore, the activation energy for inversion is probably less than 10 kcal/mol.

Discussion

Oxidation of the α -tocopherol model compound (1) in acidic acetonitrile results in the formation of the phenoxonium type ion (8). The fact that the stable cation radical (9) is oxidized more than 600 mV more anodic than the substrate (1) in dichloromethane-TFA clearly rules out the dication structure (7) for the two-electron oxidation product. Solvent effects on the difference in potentials for loss of the first and second electron have been observed in other cases; however, such effects are usually of much lower magnitude.¹⁷ The fact that it was possible to observe 7 in more acidic media and that the latter showed a different visible spectrum than 8 gives conclusive support for phenoxonium type structure for the oxidation product in acetonitrile.

The stability of 8 in acetonitrile containing TFA is remarkable. In acetonitrile containing 60 mM water, voltammetric oxidation of 1 is accompanied by the rapid formation of 6 which in the presence of strong acid rapidly rearranges to the quinone, 3.¹⁰ Under our conditions, we estimate the water concentration in dichloromethane-TFA (9:1) to be of the order of 55–60 mM, yet the half-life of 8 in that solvent system is about 30 min. Admittedly, the activity of water may be significantly diminished by the presence of TFA; however, the enhancement of stability would appear to be too great for that effect alone to be operative. It appears likely that specific solvation of 8 by TFA is responsible for the low reactivity in dichloromethane-TFA (9:1).¹⁸

The stability of the cation radical (9) in TFA or dichloromethane-TFA is even more remarkable. If we consider the ECE reaction (eq 2) we can make pre-



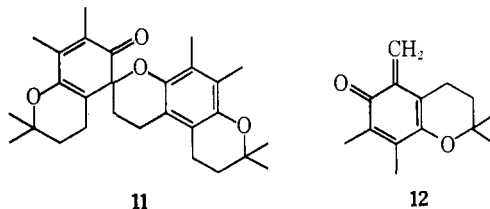
(16) The splitting was found to be field dependent.

(17) The difference in potential for the first and second electron transfers ($\Delta E^\circ = E_2^\circ - E_1^\circ$) has been determined in dichloromethane (A. J. Bard and J. Phelps, *J. Electroanal. Chem.*, **25**, in press) and in dichloromethane-acetonitrile (U. Svanholm, B. Svensmark-Jensen, and V. D. Parker, *J. Chem. Soc., Perkin Trans. 2*, in press) mixtures for the oxidation of tetra-*p*-anisylethylene. In dichloromethane ΔE° was found to be of the order of 90 mV and to vary linearly with log (per cent acetonitrile) reaching a minimum value of 0 mV in pure acetonitrile.

(18) A similar effect on stability by TFA has been observed for the thianthrene cation radical which is short lived in acetonitrile containing even low concentrations of water. Reversible cyclic voltammograms for thianthrene have been observed in TFA containing as much as 50% water: O. Hammerich, N. S. Moe, and V. D. Parker, *J. Chem. Soc., Chem. Commun.*, 156 (1972). Recent kinetic measurements for the hydroxylation of thianthrene cation radical in acetonitrile have shown that the reaction is third order in water indicating that the reactive species is a water solvated complex of the radical ion: O. Hammerich, U. Svanholm, and V. D. Parker, manuscript in preparation. Thus, the function of TFA is believed to be the replacement of water as the solvating agent leading to a stable species.

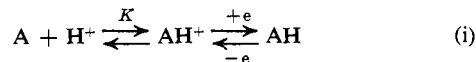
dictions of the form of the cyclic voltammogram for the substrate, 1. Proton transfers from oxygen are generally very rapid reactions. Thus, if the equilibrium concentration of 10 is finite, one would expect further electron transfer to occur during cyclic voltammetry with the ultimate result being a two-electron oxidation of 1 producing 8 via the ECE pathway. This is in fact what is observed during cyclic voltammetry in acetonitrile or acidic acetonitrile. However, even at the very slow voltage sweep rate of 15.6 mV/sec, the voltammogram of 1 in either TFA or dichloromethane-TFA (3:1) consists of a perfectly reversible one-electron redox couple. This can only be interpreted to indicate that the equilibrium constant, K_{9-10} , is very low in these media.¹⁹ The latter is also supported by the fact that the esr spectra show the presence of only 9 without contamination from the neutral radical, 10. These observations are indeed surprising in view of the fact that phenolic cation radicals in general are believed to be quite acidic, having pK_a values of the order of -5 .²⁰ Furthermore, the acidity of neat TFA may be considerably lower than that of aqueous TFA,²¹ and if the latter is indeed the case 9 must be a weak acid. A plausible reaction pathway for the slow decomposition of 9 is dissociation to 10 followed by some irreversible reaction of the phenoxy radical.

It is obvious that discussions of the reversible oxidation products of tocopherols and related chromanols must take into account the nature of the medium as well as the oxidant. There is abundant literature concerning the chemical oxidation of α -tocopherol and model compounds. Oxidation with alkaline ferricyanide^{22,23} or benzoquinone²⁴ leads to the formation of the spiro dimer, 11. This reaction has been proposed to take place by initial oxidation to the phenoxy radical, 10, which undergoes further oxidation accompanied by the formation of the quinone methide, 12.²⁵ The



quinone methide could just as well be formed by two-electron oxidation to 8 followed by deprotonation. It seems reasonable that any oxidant which functions by an electron-transfer mechanism will give as the initial

(19) In fact, calculations indicate (R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 706 (1964)) that for an equilibrium such as eq 1, a re-



versible voltammogram for the reduction of AH^+ will be obtained if K for the protonation is as low as 10^{-6} . Analogously, if K_{9-10} were as great as 10^{-6} in these solvent systems, a reversible two-electron rather than a reversible one-electron voltammetric process would be observed.

(20) E. J. Land, G. Porter, and E. Strachan, *Trans. Faraday Soc.*, **57**, 1885 (1961).

(21) M. J. Harriss and J. B. Milne, *Can. J. Chem.*, **49**, 2937, 3612 (1971).

(22) W. A. Skinner and R. M. Parkhurst, *J. Org. Chem.*, **29**, 3601 (1964).

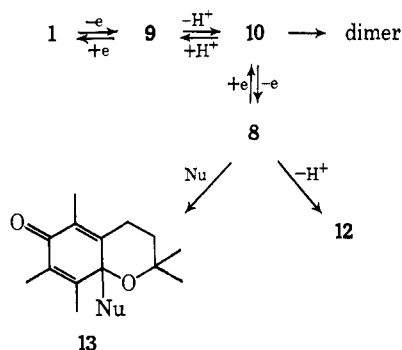
(23) W. A. Skinner and P. Alaupovic, *Science*, **140**, 803 (1964).

(24) J. L. G. Nilsson, G. D. Daves, Jr., and K. Folkers, *Acta Chem. Scand.*, **22**, 207 (1968).

(25) K. Dimroth, W. Umbach, and H. Thomas, *Chem. Ber.*, **100**, 132 (1967).

product the cation radical, **9**. Thus, the nature of the product formed after the initial reversible electron transfer is only a function of the nature of the medium in which oxidation takes place. In neutral or basic media, deprotonation of **9** would be rapid producing **10**. The fate of **10** depends upon the relative rates of further oxidation or of dimerization. Providing that further oxidation to **8** takes place another branching of pathways can occur. In the presence of water or other nucleophilic species, dienones such as **5** or **6** may be formed. Alternatively, deprotonation of **8** may occur giving the quinone methide (**12**). These various reaction pathways are summarized in Scheme I.

Scheme I



Phenoxonium ions, for example **14**, have previously been observed,²⁵ and the exchange of identity of aromatic and vinylic methyl groups in the nmr spectrum of **11** upon heating has been attributed to equilibration involving the ions, **15** and **16**.²⁶ However, in none of the previous studies of tocopherol oxidation has there been any indication of stability of such ions as **8**, and the results reported here have strong implications of support for the phenoxonium ion as an intermediate in some phenol couplings, a topic which is being actively pursued.²⁷⁻²⁹

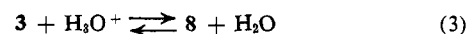
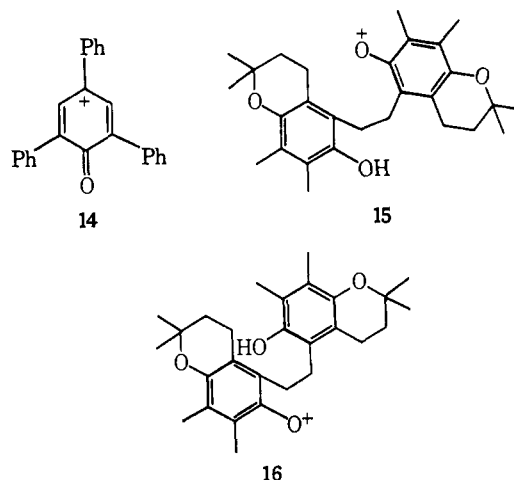
It should be pointed out that equilibrium (eq 3) lies

(26) M. Chauhan, F. M. Dean, K. Hindley, and M. Robinson, *Chem. Commun.*, 1141 (1971).

(27) D. H. R. Barton, *Chem. Brit.*, 3, 330 (1967).

(28) D. G. Hewitt, *J. Chem. Soc. C*, 1750 (1971).

(29) A. Ronlän, *Chem. Commun.*, 1643 (1971).



far to the right in acetonitrile-TFA (9:1). This is demonstrated by the fact that a solution of **3** in the latter solvent is stable and is immediately transformed to **8** upon the addition of a trace of concentrated sulfuric acid. TFA does not appear to be strong enough to affect the cyclization of **3**. Thus, the product of the decomposition of acetonitrile-TFA solutions of **8** is probably the hydroxyl dienone (**6**) which does not revert to **3** in the absence of a stronger acid.

Experimental Section

Procedures and apparatus for voltammetry and constant current coulometry have previously been described.^{12b, 20}

The α -tocopherol model compound was prepared by a standard procedure.³¹ Acetonitrile was purified by the method of Moe³² and passed over neutral alumina before use.

The nmr spectra were recorded at 60 MHz on a Varian A-60A spectrometer and at 90 MHz on a Bruker HX90E spectrometer. The spectra in $CD_2Cl_2-SbCl_5$ were recorded with CH_2Cl_2 as the internal standard, but the chemical shifts were converted to τ values. ESR spectra were recorded in sealed cuvettes on a Jeol JES-ME-1X spectrometer. Care was taken to avoid moisture especially in the experiments where deuterated media were used.

(30) O. Hammerich and V. D. Parker, *J. Chem. Soc., Perkin Trans. I*, 1718 (1972).

(31) J. I. Smith, H. E. Ungnade, H. H. Hoehn, and S. Wawzonek, *J. Org. Chem.*, 4, 311 (1939).

(32) N. S. Moe, *Acta Chem. Scand.*, 21, 1389 (1967).