# MECHANISMS OF α-TOCOPHEROL OXIDATION: SYNTHESIS OF THE HIGHLY LABILE 9-HYDROXY-α-TOCOPHERONE

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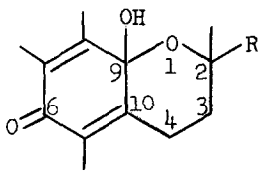
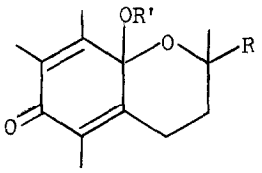
On several occasions there has been speculation regarding the existence of highly labile intermediates in the oxidation of natural chromanols, both in their capacity as tissue antioxidants and in their possible role in oxidative phosphorylation (1). We have synthesized such an intermediate, the quinone hemiacetal (I) of α-tocopherol and have found it to be, indeed, a highly labile substance.

The compound I, for which we propose the trivial name 9-hydroxy-α-tocopherone,† may be prepared by oxidation of α-tocopherol by means of tetrachloro-o-quinone in aqueous acetonitrile or N-bromosuccinimide in aqueous buffer-acetonitrile. It may be identified by the presence of a high intensity peak at 242 mμ in the ultraviolet, which shifts rapidly to the double peak




I, R = $C_{16}H_{33}$




II, R = $C_{16}H_{33}$
R' = α-tocopheryl

of α-tocopherylquinone at 265 mμ. Stability of the compound is highly de-

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† The parent compound, α-tocopherone, would then be the dienone tautomer of α-tocopherol.

pendent on pH, with an optimum half-life of 44 min. at an apparent pH of 5.4, when prepared with N-bromosuccinimide in an acetate buffer-acetonitrile mixture (2:5). From the data summarized in Fig. 1, it is evident that a small deviation from the optimum pH value in either direction effects a rapid rearrangement of I to the quinone. Using tetrachloro-o-quinone as oxidant in water-acetonitrile (2:5), a half-life of 53 min. may be realized. From such oxidation mixtures I may be extracted into petroleum ether (30-40°), in which solvent a half-life of 3-4 hours is observed. The infrared spectrum in the latter solvent shows a free hydroxyl band at 3490 $cm.^{-1}$ (2.87 $\mu$) and a carbonyl band at 1635 $cm.^{-1}$ (6.12 $\mu$); $\lambda_{max}$ 238 m$\mu$ ($\epsilon$ 12,000, petrol.); $\lambda_{max}$ 242 m$\mu$ ($\epsilon$ 12,000, aq. acetonitrile).

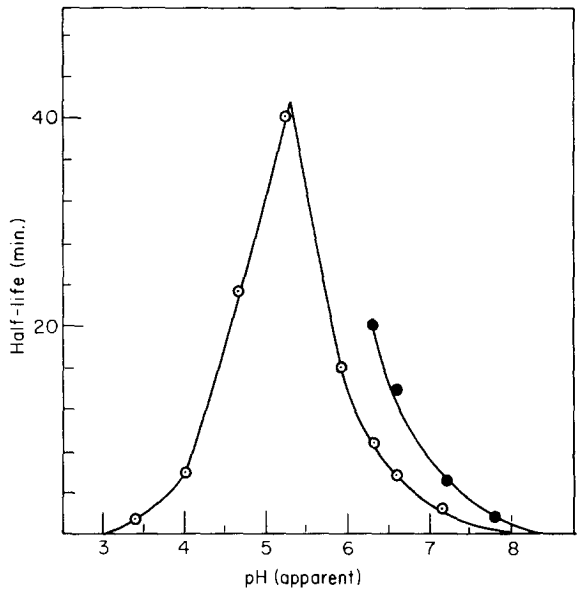


Fig. 1. Effect of pH on stability of 9-hydroxy-$\alpha$-tocopherone (I) in acetonitrile-buffer (5:2); —⊙— M/5 acetate; —●— M/15 phosphate.

Decomposition of I in petroleum ether, in alkaline or in acidic media leads to $\alpha$-tocopherylquinone. In acidic media, a small amount of a stable

dimeric substance is also formed. That I is not a dimeric substance of type II is seen by the fact that no α-tocopherol is regenerated during its decomposition and by the fact that two equivalents of oxidant are consumed in its formation. The dienone is reduced almost quantitatively to α-tocopherol by aqueous ascorbic acid, pyrogallol, sodium iodide or toluhydroquinone, but is unaffected by hydroquinone. On the other hand, α-tocopherol is oxidized by p-quinone but only very slowly by tolu-p-quinone. We therefore estimate the redox potential of I to be between +0.699 mv. and +0.645 mv. (2).

When α-tocopherol is reacted with a stable free radical such as tri-t-butylphenoxyl, two equivalents of radical are consumed per mole of substrate and the only product formed, either in polar solvents (ethanol, aqueous acetonitrile) or in aprotic solvents (benzene), is the yellow dimer first prepared by alkaline ferricyanide oxidation of α-tocopherol (3) and whose structure has recently been elucidated. (4). Free radical oxidation of α-tocopherol does not produce I, tocopherylquinone or tocopherethoxide (in ethanol). These findings lead to a more detailed picture of the pathways of oxidation of α-tocopherol:

(a) Monovalent oxidation leads to a free radical, which dimerizes and undergoes further dehydrogenation to a spirodienone-ether (4).

(b) Divalent oxidation leads to a mesomeric cation which, in the presence of nucleophiles, forms a 9-substituted-α-tocopherone. The latter undergoes further rearrangement to α-tocopherylquinone. In the absence of nucleophiles, the cationic intermediate leads to a series of stable dimers (currently under investigation) which differ from those previously reported. (3,4).

(c) In its role as antioxidant, α-tocopherol should be converted, not to tocopherylquinone, but to a dimeric end-product. Such a dimer has recently been isolated from tissues and shown to be identical to the dimer obtained by ferricyanide oxidation. (5).

(d) The isolation of tocopherylquinone from tissues (6) suggests an additional role for tocopherol (and for other chromanols), apart from that of

an antioxidant and possibly related to energy conservation. In this regard it is of interest that I is readily reduced back to α-tocopherol and that its stability is markedly enhanced in non-polar solvents, a situation comparable to the lipoid medium in which α-tocopherol exists in the cell.

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