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THE REACTION OF A α-TOCOPHEROL MODEL COMPOUND WITH KO$_2$, A NEW OXIDATION PRODUCT OF 6-HYDROXY-2,2,5,7,8-PENTAMETHYLCHROMAN[1]

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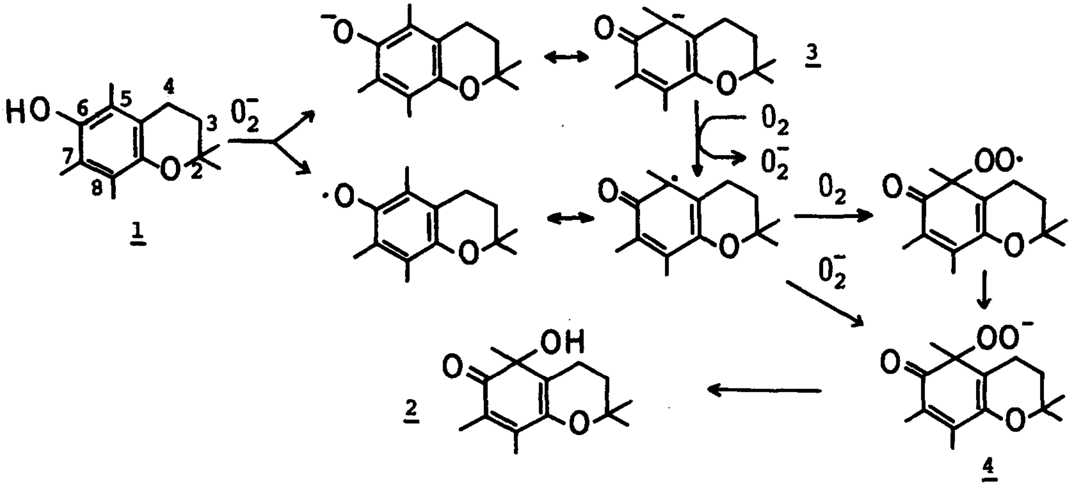
Recently, the production of superoxide anion (O$_2^-$) in a variety of biological systems has been known.[2] From the view of biological protection against O$_2^-$, the reaction of α-tocopherol with O$_2^-$ is of great interest. Nishikimi and Machlin examined the reaction of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, a α-tocopherol model compound, with O$_2^-$ generated from a xanthine-xanthine oxidase system, obtaining 2-hydroxy-2-methyl-4-(3,5,6-trimethylbenzoquinone-2-yl)butanoic acid.[3] We wish to report the reaction of 6-hydroxy-2,2,5,7,8-pentamethylchroman (1) with KO$_2$, as a source of O$_2^-$, in tetrahydrofuran (THF). This may be a more suitable model reaction than that in an aqueous solution, because α-tocopherol occurs in such hydrophobic environments of tissues as cell membrane.

1 was reacted at 0° for 8 hr with three equimolar of KO$_2$ suspended in THF. A product (2), mp 104-5°, colorless needles, was obtained in a 20% yield. It has; Mass: m/e(M$^+$) 236, UV: λ(MeOH)(nm) 249s(ϵ 5500), 327(ϵ 2800), IR: ν(KBr) (cm^{-1}) 3420, 1655, 1638, 1578, ^{1}H-NMR: δ(CDCl$_3$)(ppm) 1.34(9H,s), 1.50-1.80(2H, m), 1.82(3H,s), 1.99(3H,s), 2.00-2.70(2H,m), 3.50(1H,s), ^{13}C-NMR: δ (CDCl$_3$) (ppm) 11.4(q), 13.6(q), 15.5(t), 25.9(q), 27.3(q), 30.0(q), 31.6(t), 75.6(s), 77.7(s), 103.1(s), 122.1(s), 147.2(s), 165.2(s), 202.6(s).

The molecular ion peak of 2 (m/e 236) indicates the introduction of an oxygen atom into 1 (m/e 220). The UV and IR spectra suggest the presence of a conjugated cyclohexadienone and a hydroxyl group in the structure of 2. In the ^{1}H-NMR spectrum, there are two methyl signals attaching to sp^2 carbons (1.82 and 1.99 ppm) and a methyl signal corresponding to three methyl groups (1.34 ppm). By addition of Eu(fod)$_3$, the signal of a methyl group at 1.34 ppm shifted greatly to lower field. In the ^{13}C-NMR spectrum, the peaks of a ketonic (202.6 ppm), four quaternary sp^2 (165.2-103.1), two oxygenated quaternary (77.7 and 75.6) and two methylene carbons (31.6 and 15.5) in addition to the ones of five methyl groups are observed. The position of a hydroxylated carbon in 2 was determined by the examination of the NMR spectra of deuterium-labeled 2. In the NMR spectra of the labeled 2 derived from 5-CD$_3$-1,[4] the intensity of a singlet ^{1}H-peak at 1.34 ppm decreases from 9H to 6H and a ^{13}C-peak for a methyl carbon at 30.0 ppm can not be found. Since 7,8-unlabeled carbons in 5-CD$_3$-1 were converted to two methyl carbons attaching to two sp^2 carbons in 2, it is apparent that the hydroxylation occured at 5-position of 1. Thus, the structure is depicted as 2 in the Figure.

The reaction mechanism of the formation of 2 remains obscure. But when the reaction was carried out under an oxygen atmosphere, 2 yielded almost quantitatively. Presumably, an oxygen atom of a hydroxyl group in 2 may come from molecular oxygen. If O_2^- accept a proton from 1, perhydroxyl radical in its protonated form will dismutate to give molecular oxygen and H_2O_2.[5] The H_2O_2 will react with O_2^- to give molecular oxygen, too.[6] This seems to be similar to Moro-oka and Foote's findings that oxygen was evolved during the oxidation of 9,10-dihydroxyphenanthrene and 3,5-di-t-butylcatechol with KO_2 and that molecular oxygen took part in the oxidation.[7] In the oxidation of 1, a carbanion (3) seems to be important because 2 also arose from 1 on a t-BuOK-catalyzed oxidation in t-BuOH.[8] Interestingly, 2,4,6-tri-t-butylphenol affords a hydroperoxycyclohexadienone in a t-BuOK-t-BuOH oxidation system.[9] Probably, 2 is formed via a hydroperoxide (4). Although the protonation of O_2^- is assumed as the initial step of the reaction, the hydrogen abstraction with O_2^- can not be ruled out. A hypothetical scheme is shown below;



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