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MECHANISM OF OXYGENATION OF NAPHTHOQUINONE DERIVATIVE

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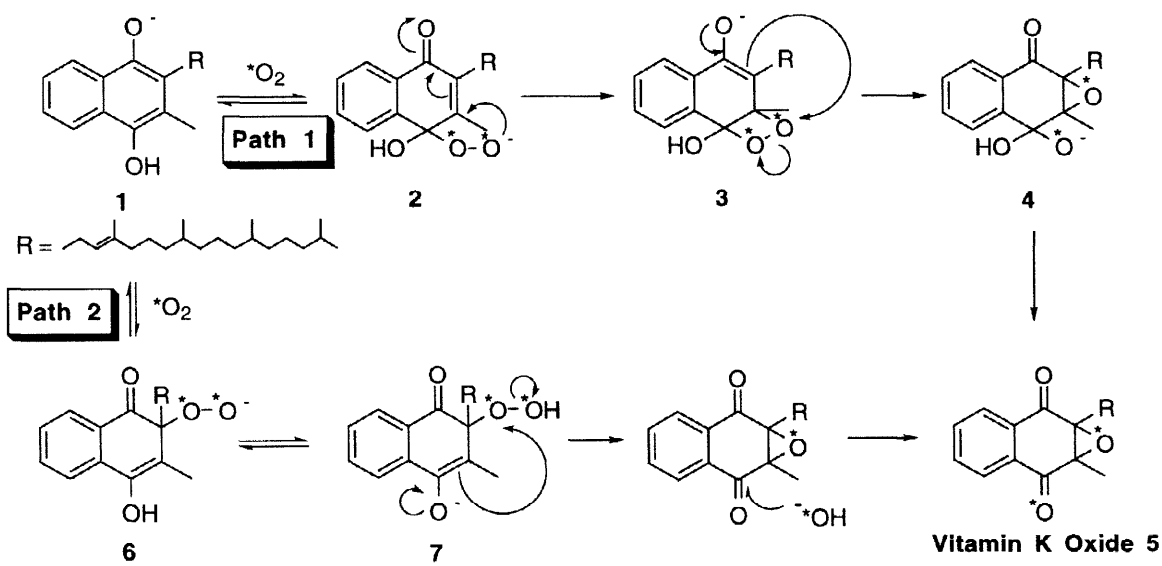
Abstract : Vitamin K in its hydroquinone form, vitamin KH_2, is transformed to vitamin K oxide concurrent with the abstraction of the γ-hydrogen of Glu leading to Gla. The nonenzymatic model supports that oxygenation of the monoanion of vitamin KH_2 can produce the peroxy anion at the 4-position yielding vitamin K oxide.

Vitamin K catalyzes carboxylation of selected glutamate residues in seven zymogen precursors to the enzymes associated with the blood clotting cascade.[1] Key features of this mechanism is found to be the rearrangement to a strong alkoxide base **4** through the dioxetane intermediate **3** using molecular oxygen (path 1), which is supported by the results of ^{18}O labeling studies of vitamin K-dependent carboxylation *in vivo*.[2] Recently, we also investigated the oxygenation reaction of vitamin K hydroquinone itself, in the absence of the enzyme.[3] Thus, when the monoanion of vitamin K hydroquinone was treated with $^{18}O_2$, the product, vitamin K oxide, carried a full atom of ^{18}O at the epoxide oxygen and partial incorporation (34%) of a second atom of ^{18}O at the carbonyl oxygen. This result was most reasonably ascribed to the dioxetane mechanism (path 1). However, molecular oxygen can also add to the 2-position of vitamin KH_2 anion yielding the hydroperoxy anion **6** which might produce vitamin K oxide (path 2),[4] even though formation of hydroxide



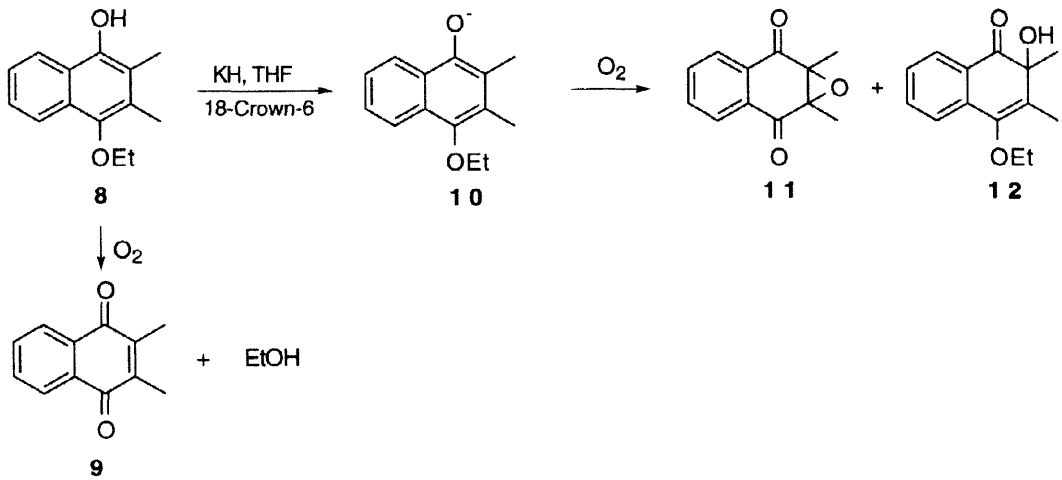
Scheme 1

PII: S0040-4039(98)00714-X

anion might be unfavorable under aprotic conditions. Incorporation of ^{18}O into vitamin K oxide would then be resulted in label exchange between ^{18}O labeled hydroxide and the product.[5] This path could not be ruled out and the appropriate control reactions remained to be conducted.

In the present study, we have investigated the oxygenation behavior of a naphthohydroquinone with a protected hydroxy group, since the result of this experiment unambiguously differentiate between the mechanisms shown in Scheme I. To prepare the ethyl ether **8**, the known monoacetate[6] was ethylated by treatment with potassium hydride followed by ethyl iodide. The ethoxy acetate was then hydrolyzed under an inert atmosphere with sodium hydroxide, yielding the oxygen-sensitive ethyl ether **8**.

Since the biological transformation of vitamin K oxide appears to be shielded from water by the enzyme or membrane environment, we performed the oxygenation reaction in aprotic condition.[7] Thus, when a solution of potassium naphthoxide **10** in THF, from reaction of the corresponding alcohol **8** and 1 equivalent of KH, was stirred under an atmosphere of oxygen at room temperature for 2 h in the presence of 18-crown-6. After treatment with saturated NH_4Cl and KCl solution, two major products were detected by the GC trace. Purification of the mixture by chromatography provided the epoxy quinone **11** in 34% yield and 2-hydroxy adduct **12** in 45% yield.[8] The epoxy quinone **11** must arise from formation of the peroxy anion intermediate



Scheme 2

at the 4-position, while the 2-hydroxy product **12** could arise from the 2-peroxy anion intermediate.[8] Therefore, the addition of oxygen in THF with 18-crown-6 might yield the oxygenation products in the 2- (path 2) and 4-position (path 1) without regioselectivity. This regioselectivity observed in the oxygenation might be rationalized in terms of the stability of the peroxy anion intermediates. Since it is known that the potassium ion strongly associates with crown ether, the peroxy anion intermediate would be naked, the resulting free peroxy anion **14** at the 2-position might experience electronic repulsion against the carbonyl group, and the peroxy anion **13** at the 4-position is also unstable by electron repulsion against oxygen of ethyl ether in THF with 18-crown-6.[9] Meanwhile, it was also interesting to know that the ethyl ether were oxidized to the dimethyl naphthquinone **9** and by product, ethanol.

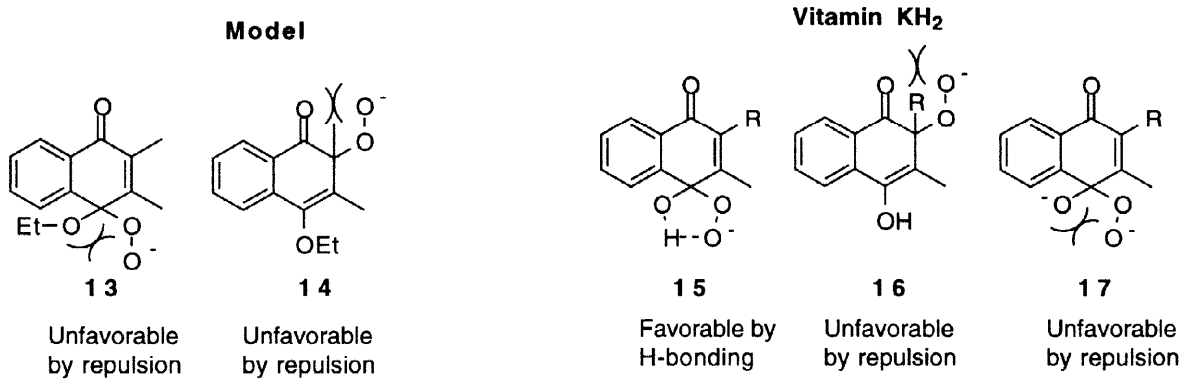
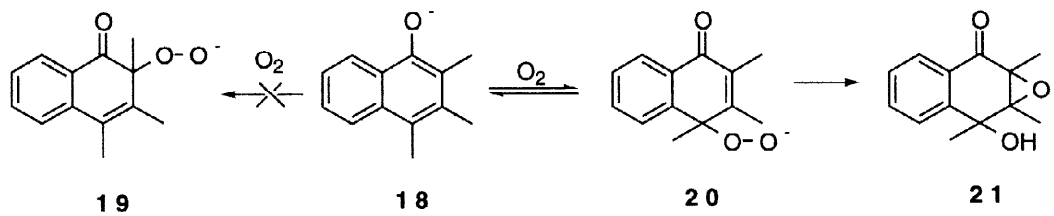


Figure 1

However, there is important difference between the model **8** and vitamin K hydroquinone. In the vitamin K, the resulting free peroxy anion **16** at the 2-position might experience electronic repulsion against the carbonyl group, whereas the peroxy anion **15** at the 4-position is stabilized by hydrogen bonding with gem-hydroxy group. Therefore, the addition of oxygen might be preferred in the 4-position. This prediction too is supported by the earlier results,[9] where oxygenation of potassium 2,3,4-trimethyl-1-naphthoxide **18** in THF with 18-crown-6 gave rise to the corresponding 2,3-epoxy-4-hydroxy adduct **21** in nearly quantitative yield, through the 4-hydroperoxide intermediate **20**, since 2-hydroperoxide could experience electronic repulsion against the carbonyl group.



Scheme 3

Vitamin KH_2 can ionize in the enzymatic environment to produce equilibrium concentration of dianion (pK_{a1} = 9.3, pK_{a2} = 10.6).[11] Therefore, it has been postulated that oxygenation of the dianion can lead by a similar path to the geminal dialkoxide, which is expected to be a very strong base capable of removing a proton from Glu to enable carboxylation.[2b] However, our results show that the formation of dialkoxide is not plausible. If molecular oxygen reacts with vitamin K^{2-} at the 4-position yielding 4-peroxy dianion adduct **17**, the latter is also unstable by electron repulsion against oxide anion as shown in Figure 1.

Acknowledgment

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5. When a solution of vitamin K oxide in THF was stirred with $H_2{}^{18}O$ in the presence of base or acid at room temperature, the oxygens in the carbonyl groups were rapidly exchanged with oxygen-18.

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8. The spectral data of epoxy quinone **11** were identical with an authentic sample obtained by epoxidation of 2,3-dimethyl-1,4-naphthoquinone. We could not isolate the 2-hydroperoxide. Chromatography of the crude product on silica gel provided the 2-hydoxy product **12**. Data for **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (t, J=7.1 Hz, 3H),1.53 (s, 3H), 2.02 (s, 3H), 3.82 (s, ex, 1H), 1.14 (q, J=7.2, 2H), 7.34 (td, J = 7.6, 1.3, 1H), 7.43 (td, J = 7.6, 0.9, 1H), 7.65 (d, J=7.6, 1H), 7.69 (d, J = 7.4, 1H). The ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.5 (q, J=129 Hz), 15.8 (q, J=128 Hz), 34.1 (q, J=130 Hz), 69.4 (t, J=146 Hz), 76.1 (s), 117.3 (s), 124.1 (dd, J=162, 8 Hz), 125.1 (dd, J=159, 8 Hz), 127.1 (s), 127.6 (dd, J=161, 8 Hz), 130.1 (dd, J=161, 8 Hz), 143.4 (s), 165.2 (s), 205.7 (s). IR (neat): 3500 (br s), 1660 (vs),. Mass: *m/e* (relative intensity) 232 (M^+, 11), 204 (10), 189 (40), 161 (100). Exact Mass calculated for $C_{14}H_{16}O_3$: 232.1099. Found: 232.1099.

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