Tetrahedron Letters No. 19, pp 1693 - 1696. 0040-4039/79/0501-1693$02.00/0

THE REACTION OF SUPEROXIDE ION WITH VITAMIN K_1 AND ITS RELATED COMPOUNDS

Isao Saito, Toshiaki Otsuki, and Teruo Matsuura
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University
Kyoto 606, Japan

The reaction of potassium superoxide with vitamin K_1 and its related compounds in the presence of crown ether gave the corresponding 2,3-oxide and phthalic acid. The oxidative cleavage of oxirane ring by superoxide ion has been observed with vitamin K_1 2,3-oxide and certain epoxides.

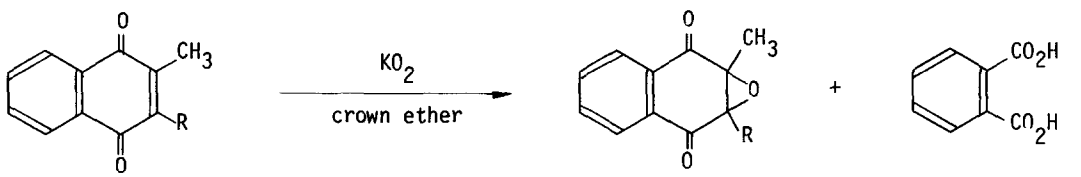
In recent years there has been considerable interest concerning the chemistry of superoxide ion, O_2^-, as a possible active species for certain biological oxidations.[1] The deleterious effects of O_2^- in biological systems have also become increasingly evident.[1] The reaction of O_2^- with vitamin K_1 is of particular interest not only from the view point of the protection against O_2^- in biological systems but also as a model for the microsomal conversion of the vitamin to its 2,3-oxide catalyzed by epoxidase.[2] We wish to report our observation on the reaction of vitamin K derivatives with potassium superoxide (KO_2) dissolved in organic solvents by complexation with crown ethers. Before we initiated an investigation on the reaction, the rate constants of the reversible electron-transfer reactions between O_2^- and vitamin K_1 or 1,4-naphthoquinones in aqueous solutions have been reported.[3] However, nothing has been known of the chemistry of the reactions.

In a typical experiment, a solution of 2,3-dimethyl-1,4-naphthoquinone (1) (1 mmol) in dry benzene (20 ml) was added to a mixture of powdered potassium superoxide (4 mmol) and 18-crown-6 ether (1 mmol) dissolved in dry benzene (40 ml). The mixture was vigorously stirred under the stream of oxygen for 1 h. The solution was acidified with 2N HCl and the mixture was extracted with saturated $NaHCO_3$. The aqueous extracts were acidified and extracted with ether to give phthalic acid (2) (19%). The benzene layer was dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by preparative TLC (silica gel) to give the 2,3-oxide 3

(7%).

In control experiments 1 was oxidized in the presence of Na_2O_2 or potassium acetate in place of KO_2 under identical conditions. In both cases 1 was recovered quantitatively. The reaction of 1 with KOH-crown ether under oxygen atmosphere was sluggish and gave only small amounts of phthalic acid 2 even after 3 h. These results indicate that $O_2^{\cdot-}$ is indeed involved in the reaction, and that the base-catalyzed autoxidation of 1 is not involved to any substantial extent.

The reaction of $O_2^{\cdot-}$ with vitamin K_1 (4) or its model compound 5 gave essentially the same result (Table 1). Vitamin K_1 yielded the corresponding 2,3-oxide 6 (16%) and phthalic acid (2) (19%). In the case of 5 cinnamic acid and benzoic acid resulting from the degradation of the side chain were obtained in addition to 2 and 7 (entry 6 and 7). As evident from Table 1, the yield of phthalic acid (2) was increased by prolongation of the reaction time, suggesting that 2 was formed by further oxidation of the 2,3-oxide with $O_2^{\cdot-}$. In fact, 2,3-epoxy-1,4-naphthoquinones (3,6,7) were oxidized slowly by $O_2^{\cdot-}$ under the conditions to give 2 and the products deriving from side chain degradation (entry 8-10). Under conditions in which 3 or chalcone oxide (entry 11) was oxidized, styrene oxide and stilbene oxide were inert toward $O_2^{\cdot-}$, indicating that an adjacent carbonyl group is necessary for the oxidative cleavage of the oxirane ring by $O_2^{\cdot-}$.[4]



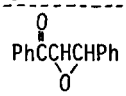
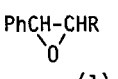
1, R = CH_3
4, R = phytyl
5, R = $CH_2CH{=}CHPh$

3, R = CH_3
6, R = phytyl
7, R = $CH_2CH{=}CHPh$

2

The chemical reactivity of $O_2^{\cdot-}$ has been a subject of much current controversy.[5] Recent work by Sawer et al.,[6] has claimed the inertness of $O_2^{\cdot-}$ toward electron-rich substrates as an oxidizind agent, although its nucleophilicity and its reducing power seem to be well established.[5] In the present case, neither 1 nor 4 has acidic hydrogens which might be removed

Table 1 Reaction of Vitamin K_1 and its Related Compounds with Potassium Superoxide in Benzene[a]

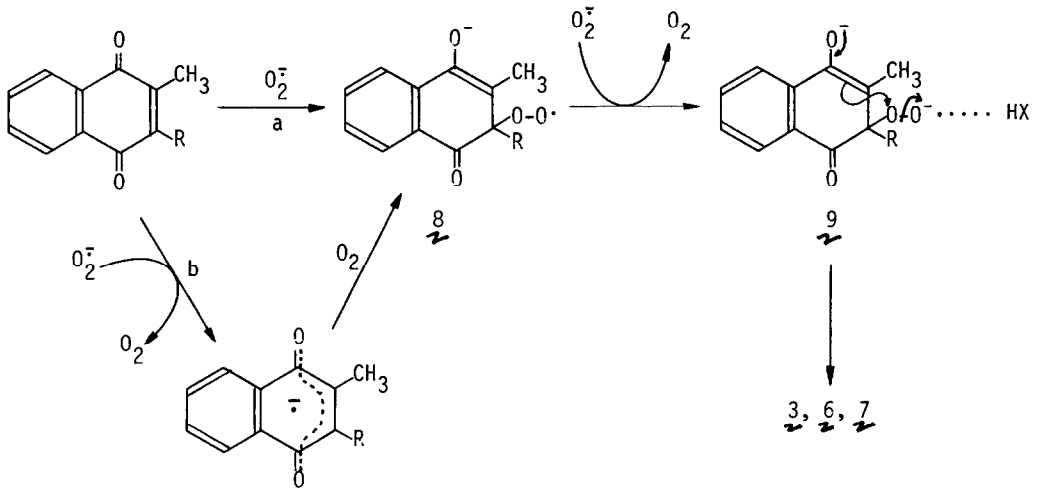
Entry	Substrate (mmol)	KO_2 mmol	Reaction time	Products (%)[b]	Recovered substrate (%)
1	1 (1)	4 mmol	10 min	2 (16) 3 (16)	1 (15)[d]
2	1 (1)	4	1 h	2 (19) 3 (7)	-[d]
3	1 (1)[c]	4	2 h	2 (23) 3 (5)	-[d]
4	4 (1)	4	1 h	2 (19) 6 (16)	-[d]
5	4 (1)	4	3 h	2 (21) 6 (12)	-[d]
6	5 (1)	4	0.5 h	2 (3) 7 (8) $PhCH{=}CHCO_2H$ (4)	-[d]
7	5 (1)	4	4 h	2 (19) $PhCH{=}CHCO_2H$ (8) $PhCO_2H$ (3)	-[d]
8	3 (1)	4	8 h	2 (43) CH_3CO_2H	3 (46)
9	6 (0.75)	1.5	5 h	2 (10)[d]	6 (54)
10	7 (1)	4	4 h	2 (23) $PhCH{=}CHCO_2H$(4) $PhCH{=}CHCH_2CO_2H$(2)	7 (15)[d]
11	 (1)	4	7 h	$PhCO_2H$ (55)	-
12	 (1) R = H, Ph	4	7 h	No reaction	-

[a]The reactions were carried out under oxygen atmosphere at room temperature. Under nitrogen atmosphere the reactions were much slower but gave essentially the same results. [b]The product was identified by comparison with the authentic sample. [c]In dry pyridine. [d]A complex mixture of products has been obtained.

by O_2^-. In addition, the reaction of 1 with O_2^- in rigorously dry pyridine also proceeded to give the same products (entry 3). The results indicate that the proton transfer to O_2^- is not involved at least in the initial step of the reaction. We suggest the following mechanism involving 8 as an intermediate, which may be formed by direct attack of O_2^- to the electron-deficient double bond (path a) or by an electron transfer from O_2^- to the naphthoquinone (path b) (Scheme I).[3,7] Electron transfer from O_2^- to 8 will give 9 which subsequently undergoes ring closure to give the 2,3-oxide 3 exactly in the same manner as in the epoxidation of 1 with hydroperoxy anion.[8] The mechanism of the oxidative cleavage of the oxirane ring is not clear. However, nucleophilic attack of O_2^- on the oxirane carbon may be responsible for the cleavage. In conclusion, the results described here indicate that once O_2^- is produced in biological

systems, it rapidly reacts with vitamin K derivatives to give the corresponding 2,3-oxide and phthalic acid.[9]

Scheme I



REFERENCES AND NOTES

1. A. M. Michelson, T. M. McCord, and I. Fridovich, "Superoxide and Superoxide Dismutases", Academic Press, New York, N. Y., 1977; I. Fridovich, in "Free Radicals in Biology", W. A. Pryor ed., vol 1, Academic Press, New York, N. Y., 1976, p. 239.
2. It has recently been proposed that the liver microsomal conversion of vitamin K_1 to its 2,3-oxide by molecular oxygen is coupled to the vitamin K_1-dependent carboxylation occurring in microsomes. See, J. W. Suttie, A. E. Larson, L. M. Canfield, and T. L. Carlisle, Federation Proc., 37, 2605 (1978); R. G. Bell, ibid., 37, 2599 (1978).
3. P. S. Rao and E. Hayon, J. Phys. Chem., 77, 2274 (1973), 79, 397 (1975); K. B. Patel and R. L. Willson, Trans. Faraday Soc., 69, 814 (1973).
4. For an analogous reaction with O_2^-, see J. San Filippo, Jr., C-I, Chern, and J. S. Valentine, J. Org. Chem., 41, 1077 (1976).
5. E. Lee-Ruff, Chem. Soc. Rev., 6, 195 (1977); C-I, Chern, D. C. Dicosimo, R. De Jesus, and J. San Filippo, Jr., J. Am. Chem. Soc., 100, 7317 (1978), and references therein.
6. D. T. Sawyer, M. J. Gibian, M. M. Morrison, and E. T. Seo, J. Am. Chem. Soc., 100, 627 (1978).
7. Recently O_2^- has been shown to oxidatively cleave the double bond of electron-poor olefins such as cyano- and nitro olefins probably through an electron transfer process. See I. Rosenthal and A. A. Frimer, Tetrahedron Lett., 2805 (1976); A. A. Frimer, I. Rosenthal, and S. Hoz, ibid., 4631 (1977).
8. R. Hiatt, in "Organic Peroxides", D. Swern ed., vol 2, Wiley, New York, N. Y., 1971, p. 64.
9. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan.

(Received in Japan 2 February 1979)