Epoxidation of Vitamin K_3 by Electrochemically Generated Hypohalogen Acids

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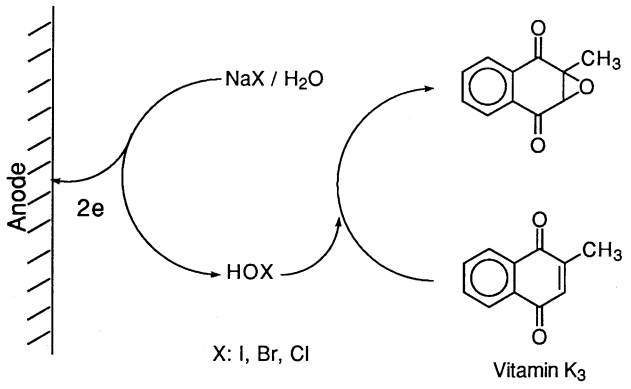
The epoxidation of vitamin K_3 was carried out using electrochemically generated hypohalogen acids HOX in organic solvent-water containing halide salts. The electroepoxidation in CH_3CN-H_2O-NaI system led to the formation of the epoxide in good yield.

Epoxide of vitamin K which plays an important role as antimicrobial and antitumor agent in metabolic processes is noted,[1] and its synthesis is also interesting.[2] On the other hand, the synthesis of organic compounds using electrochemically generated species is a current topic in synthetic organic chemistry.[3] About the epoxidation, simple olefin such as propene,[4] more complex olefins,[5] and cyclic olefin[6] are converted to corresponding epoxides. However, there have been no report on the electrochemical epoxidation of vitamin K possessing structure of quinone. In this paper we report the first epoxidation of vitamin K_3 using electrochemically generated hypohalogen acids HOX in organic solvent-water-halide salt systems.



The current-potential curves of 0.1 mol dm^{-3} halide salt NaI, NaBr, and NaCl were measured by a linear sweep voltammetry in CH_3CN-H_2O (3:7) solution on platinum disk electrode (diameter = 3mm). The controlled-potential electrolysis was performed in a divided cell equipped with a platinum plate anode (2 × 3 cm), a glassy carbon plate cathode (2 × 3 cm), an SCE reference electrode, and a glass filter diaphragm. The electrochemical epoxidation of 0.1 mmol vitamin K_3 was carried out in organic solvent-water solution (10 cm^3) containing halide salts at room temperature under an atmosphere of argon. After passing electricity of 2F mol^{-1}, the reaction mixture was extracted with ether, and the extracts were washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was analyzed by reversed phase HPLC (GL Sciences, Inertsil ODS, 250×4.6 cm).

As shown in Figure 1 when the current-potential curves of the halide salts in CH_3CN-H_2O (3:7) solution were measured, the anodic current based on two-electron oxidation of halide ion X^- to halogen X_2 was observed. The halide ions were oxidized at ca. 0.3 V (I^-), 0.7 V (Br^-), and 1.2 V (Cl^-). In the presence of water the halogen X_2 formed produces hypohalogen acid HOX immediately.[7] The halide salts play an important role as a supporting electrolyte as well as a source of HOX in this reaction system.

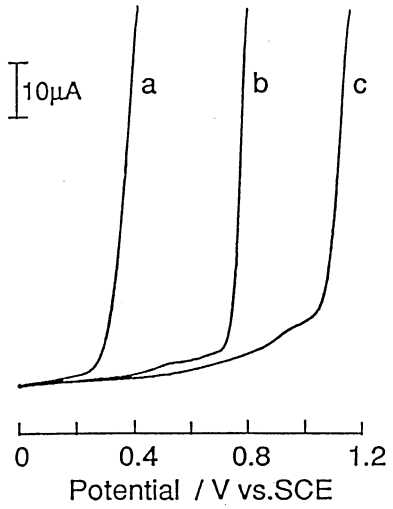


Figure 1. The current-potential curves of 0.1 mol dm^{-3} halide salt NaI (a), NaBr (b), and NaCl (c) in CH_3CN-H_2O (3:7) solution on platinum disk electrode. Scan rate : 100 mV s^{-1}.

Since HOX may be produced in electrolytic cell in aqueous solution containing organic solvent, we attempted the epoxidation of the vitamin K_3 using electrochemical technique. Most of the controlled-potential electrolyses of 0.1 mmol vitamin K_3 in organic solvent-water containing halide salts carried out in a divided cell to avoid the transfer of the substrate and product to a cathode. The results are summarized in Table 1.

Using NaBr or NaI as a halide salt, vitamin K_3 epoxide was obtained in high yields, while using NaCl the electrolysis gave appreciably low yield and the vitamin K_3 was recovered (Entries 1, 2, and 3). These results are in contrast to that of the cyclohexene carboxylate derivative, which did not give corresponding epoxide derivative in aqueous NaI solution.[6] Use of NaI as a halide salt is desirable for the electrochemical epoxidation of vitamin K_3 from the standpoint of the yield of the epoxide and the oxidation potential of iodide ion I^-.

The electrolysis of the vitamin K_3 in an undivided cell reduced the yield of the epoxide remarkably (Entry 4). This result can be explained since the vitamin K_3 and the corresponding epoxide are reduced to hydroquinone type at cathode (reduction peak potential = -0.8 V and -1.3V in 0.1mol dm^{-3} Bu_4NBF_4-CH_3CN).

Decrease of the concentration of NaI resulted in the lowering of the epoxide yield (Entry 5). The electrolysis at the high concentration of NaI above 0.5 mmol provided the epoxide in good yield (Entries 3, 6, and 7). When the electricity of 0.5 F per mol of the halide salt passed in the reaction system, the yield of the epoxide decreased (Entry 8). The epoxidation of the vitamin K_3 may successfully take place when the iodine I_2 is existent enough to produce HOI in the reaction system.

Increase of the content of CH_3CN from 3 cm^3 to 7 cm^3 suppresses the production of the epoxide (Entries 9 and 10). Furthermore the electroepoxidation in solutions containing organic solvents immiscible with water such as 1,2-dichloromethane and cyclohexane did not afford the epoxide with recovering the vitamin K_3. (Entries 11 and 12). These results

Table 1. Electrochemical Epoxidation of Vitamin K_3 in Organic Solvent-Water-Halide Salt System[a]

Entry	Halide Salt (mmol)	Solvent (cm^3 : cm^3)	Elec. Potential (V vs. SCE)	Electricity[b] (F mol^{-1})	Yield of Epoxide[c] (%)
1	NaCl (0.5)	CH_3CN - H_2O (3 : 7)	1.5	2.0	6
2	NaBr (0.5)	CH_3CN - H_2O (3 : 7)	1.0	2.0	89
3	Na I (0.5)	CH_3CN - H_2O (3 : 7)	0.5	2.0	98
4	Na I (0.5)	CH_3CN - H_2O (3 : 7)	0.5	2.0	29[d]
5	Na I (0.1)	CH_3CN - H_2O (3 : 7)	0.5	2.0	61
6	Na I (0.6)	CH_3CN - H_2O (3 : 7)	0.5	2.0	98
7	Na I (1.0)	CH_3CN - H_2O (3 : 7)	0.5	2.0	100
8	Na I (0.5)	CH_3CN - H_2O (3 : 7)	0.5	0.5	59
9	Na I (0.5)	CH_3CN - H_2O (5 : 5)	0.5	2.0	78
10	Na I (0.5)	CH_3CN - H_2O (7 : 3)	0.5	2.0	38
11	Na I (0.5)	CH_2Cl_2 - H_2O (3 : 7)	0.5	2.0	0
12	Na I (0.5)	Cyclohexane - H_2O (3 : 7)	0.5	2.0	1
13	Na I (0.5)	DMF - H_2O (3 : 7)	0.5	2.0	72
14	Na I (0.5)	CH_3OH - H_2O (3 : 7)	0.5	2.0	0

[a]Electrolyses were carried out as described in the text. [b]The electricity passed was based on the halide salts. [c]Yield was based on the vitamin K_3. [d]Electrolyses were carried out in an undivided cell.

suggest that the increase of an organic phase or the use of lipophilic solvent suppresses the formation of HOI because most of the generated iodine moves into the organic phase.

In aqueous solution containing DMF which is amphiphilic solvent, the epoxide was obtained in 72% yield (Entry 13). On the other hand, the electroepoxidation in the CH_3OH-H_2O system did not afford the epoxide (Entry 14). It is assumed that the reaction of HOI with methanol occurs preferentially.[7,8]

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