

Decomposition of Sevoflurane by Sodalime

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ABSTRACT

Stability of sevoflurane (fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether), a new inhalational anesthetic, in sodalime was examined, and the products of their reaction were identified and quantitated.

Five reaction products were identified: fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether, a dehydrofluorination product of sevoflurane which is contained as an impurity in sevoflurane preparations, fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether, a methylation product of fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether and/or sevoflurane, fluoromethyl 2-methoxy-2,2-difluoro-1-(difluoromethylene)ethyl ether and two isomers of fluoromethyl 2-methoxy-2-fluoro-1-(trifluoromethyl)vinyl ether, dehydrofluorination products of fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether.

In a closed anesthetic circuit with sodalime connected to a model lung, fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether increased and reached a plateau. Fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether increased linearly and other substances were detected only in a trace amount.

In the semi-closed anesthetic circuit with sodalime supplied with 6 liters/min fresh gas flow, no reaction products were detected except fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether, which showed a maximum concentration of 2 and 4 ppm when the feeding concentration of sevoflurane was 1.7 and 2.7%, respectively.

It is known that fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether is a weak anesthetic with $AC_{50}=3.58\%$, $LC_{50}=10.17\%$ and $AI=2.84$.

These results indicate that sevoflurane can be used with sodalime in a semi-closed anesthetic circuit.

Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether) is a newly developed volatile inhalational anesthetic^{1,3)}. Since the agent has a low blood/gas partition coefficient of 0.6⁶⁾, it is expected to show a rapid induction and recovery.

Some inhalational anesthetics react with sodalime, a common carbon dioxide absorber. Trichloroethylene, for example, is dehalogenated to yield a toxic amount of dichloroacetylene²⁾. Halothane is also degraded through dehalogenation into a small amount of

difluorochlorobromoethylene and trifluorochloroethane⁵⁾.

Sodalime contains 3~5% sodium hydroxide and potassium hydroxide. Therefore, halogenated alkyls undergo alkaline hydrolysis in the presence of sodalime (nucleophilic)⁴⁾ in addition to the abovementioned dehalogenation.

Since inhalational anesthetics are commonly used with sodalime, it is important to confirm their stability and safety in the presence of sodalime.

In this study, the stability of sevoflurane in

the presence of sodalime was examined using anesthetic circuit with model lung. Identification of the reaction products, manner of the reaction, and safety of the products are discussed.

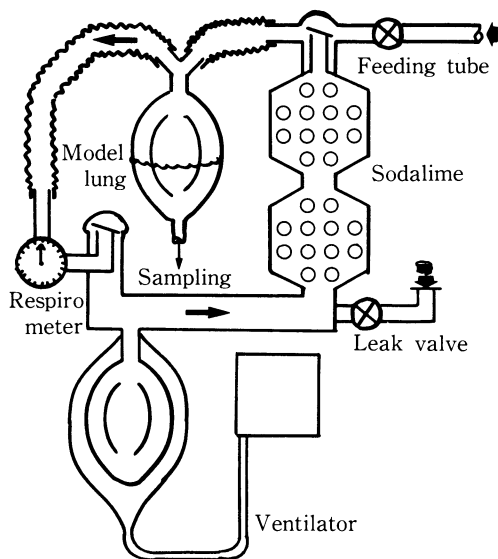


Fig. 1. Diagram of anesthetic circuit used in this study

METHODS

1. REAGENTS:

Sevoflurane was provided from Maruishi Pharmaceutical Co. Sodalime was purchased from Wako Pure Chemical Industries, Ltd. or Katayama Chemical Co., and carbon dioxide from Mitsubishi Chemical Industries. All the other reagents were of the highest grade commercially available.

2. IDENTIFICATION OF DEGRADATION PRODUCTS OF SEVOFLURANE BY SODALIME:

Sevoflurane was reacted in a test tube with sodalime at 120°C for 3 hr, and the reaction fluid was subjected to quantitative analysis.

3. DEGRADATION EXPERIMENT IN AN ANESTHETIC CIRCUIT USING A MODEL LUNG:

(1) Closed circuit system: A five liter rubber bag made elastic with rubber bands was used as a model lung, to which an anesthetic circuit (Dräger Co.) was connected (Fig. 1). Ventilation of 6 liters/min (12 times/min \times 500 ml) was obtained using a Mark II respirator of Bird Co. The system was filled with oxygen and 0.6, 1.7, or 2.7% sevoflurane which was vaporized using a sevoflurane vaporizer manufactured by Aco-

ma Medical Equipment Co. Double canister was packed with 1.6 kg of sodalime, and the gases in the system were circulated.

Carbon dioxide was fed at 200 ml/min through the feeding tube of the anesthetic machine. In some experimental systems, carbon dioxide was not fed and 100 ml of distilled water was added to the canister before the experiment in order to observe effect of water. The gas in the system was collected from the model lung and examined for the concentrations of sevoflurane and its degradation products.

(2) Semi-closed circuit system: The same anesthetic system was used, and 4 liters/min of nitrous oxide, 2 liters/min of oxygen and 0.2 liters/min of carbon dioxide were fed through the feeding tube of the anesthetic machine with 1.4 or 2.7% of sevoflurane.

4. REACTION OF SEVOFLURANE WITH METHANOL:

Sevoflurane was allowed to react with methanol in the presence of sodium hydroxide in the test tube, and the reaction liquid was qualitatively analyzed.

According to this study, mass spectrogram showed four reaction products having methoxy radical in the molecules (Fig. 4). It has been reported that halogenated anesthetics can react with sodium methoxide⁷. These results suggest that methanol is produced in this reaction system and reacts with sevoflurane and/or its metabolite.

5. QUALITATIVE ANALYSIS: Qualitative analysis was made with a gas chromatograph-mass spectrometer (Shimazu QP-1000) equipped with a 3 m column packed with DOP. Thirty ml/min of helium was used as carrier gas. Ion source temperature was set at 250°C and the ionizing energy was 70 eV.

6. QUANTITATIVE ANALYSIS: Quantitative analysis was performed with a gas chromatograph (Shimazu GC-4A) equipped with a flame-ionization detector and a 5 m column packed with DOP. Fifty ml/min of helium was used as carrier gas. The column temperature was 100°C.

RESULTS

1. ANALYSIS OF SEVOFLURANE:

A gas chromatogram of sevoflurane used in this study is shown in Fig. 2. The agent contained 10 ppm of fluoromethyl 2,2-difluoro-1-

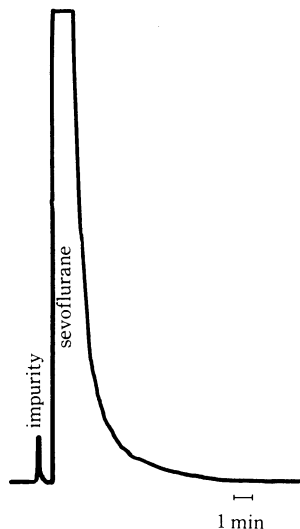


Fig. 2. Gas chromatogram of sevoflurane used in this study. Four ppm of fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether was contained as a impurity.

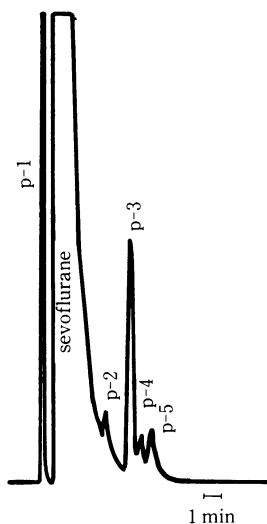


Fig. 3. Gas chromatogram of sevoflurane after reaction with sodalime for 3 hr at 120°C

(trifluoromethyl)vinyl ether as impurity.

2. IDENTIFICATION OF REACTION PRODUCTS OF SEVOFLURANE WITH SODALIME (QUALITATIVE ANALYSIS BY GC-MS):

Fig. 3 shows a gas chromatogram of sevoflurane after reaction with sodalime in a test tube at 120°C for 3 hr. The chromatogram showed six peaks including sevoflurane. These peaks excluding sevoflurane were designated p-1 to p-5 from the shortest to the longest retention time.

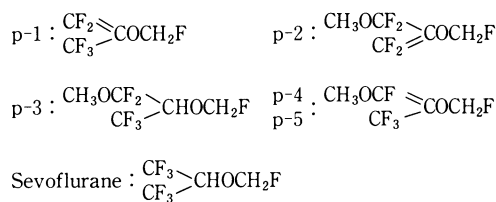
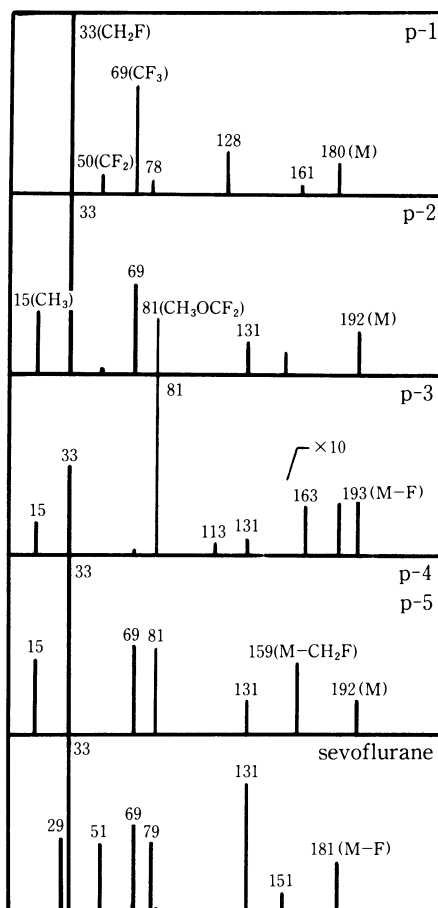


Fig. 4. Mass spectrogram of decomposition products

15:CH₃, 33:CH₂F, 50:CF₂, 69:CF₃, 81:CH₃OCF₂, 131:CH₂FOCHCF₃, 163:CH₃OCF₂CHCF₃, 180:M(p-1), 192:M(p-2), M(p-4), M(p-5)

A mass spectrogram of each substance is shown in Fig. 4. P-1 showed same spectrogram of impurity. A mass chromatogram of fragment ion of methyl (M/z 15) is shown in Fig. 5 with those of other fragment ions. From these spectrogram the substances were identified as follows:
 p-1: fluoromethyl 2,2-difluoro-1-(trifluoromethyl) vinyl ether (CF₂C(CF₃)OCH₂F),

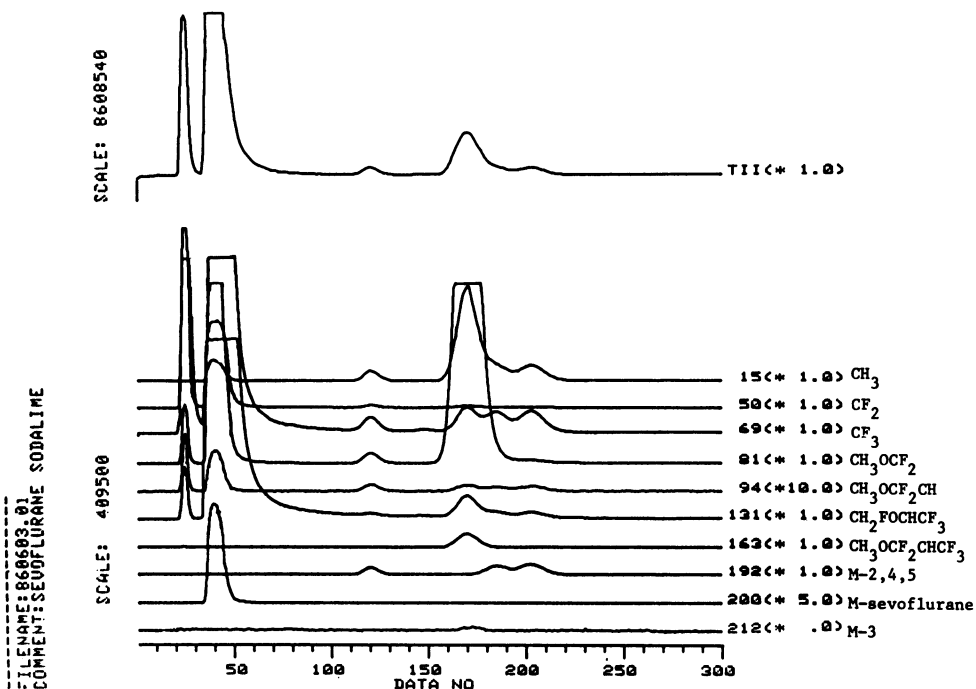


Fig. 5. Mass chromatogram of sevoflurane after reaction with sodalime for 3 hr at 120°C.

15:CH₃, 50:CF₂, 69:CF₃, 81:CH₃OCF₂, 94:CH₃OCF₂CH, 131:CH₂FOCHCF₃, 163:CH₃OCF₂CHCF₃, 192:M(p-2), M(p-4), M(p-5), 200:M(sevoflurane), 212:M(p-3)

p-2: fluoromethyl 2-methoxy-2,2-difluoro-1-(difluoromethylene)ethyl ether (CH₃OCF₂C(CF₂)OCH₂F),

p-3: fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (CH₃OCF₂CH(CF₃)OCH₂F),

p-4: fluoromethyl 2-methoxy-2-fluoro-1-(trifluoromethyl)vinyl ether (CH₃OCFC(CF₃)OCH₂F),

p-5: fluoromethyl 2-methoxy-2-fluoro-1-(trifluoromethyl)vinyl ether (CH₃OCFC(CF₃)OCH₂F),

P-4 and p-5 showed nearly identical mass spectrographic profiles and are probably cis and trans forms of CH₃OCFC(CF₃)OCH₂F.

3. REACTION IN THE CLOSED ANESTHETIC CIRCUIT USING A MODEL LUNG:

Without sodalime in the system, reaction products were not found. In the presence of sodalime, fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (p-1) showed a transient increase, but this concentration reached a plateau or slightly decreased. On the other hand,

fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3) increased linearly. The concentration of these degradation products was about two to three times greater when carbon dioxide was added than when it was not added (Fig. 6). The products also increased without carbon dioxide when distilled water was added in advance (Fig. 6). The concentration of these generated substances was proportional to the concentration of sevoflurane (Fig. 7). Other products were not detected.

4. REACTION IN THE ANESTHETIC SEMI-CLOSED CIRCUIT USING A MODEL LUNG:

Fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (p-1) increased to 2 ppm and stabilized when 1.4% of sevoflurane was fed and when 2.7% sevoflurane was fed, it stabilized at 4 ppm (Fig. 8). Fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3) was not detected in this system.

5. REACTION OF SEVOFLURANE WITH METHANOL:

Fig. 9 is gas chromatogram of sevoflurane af-

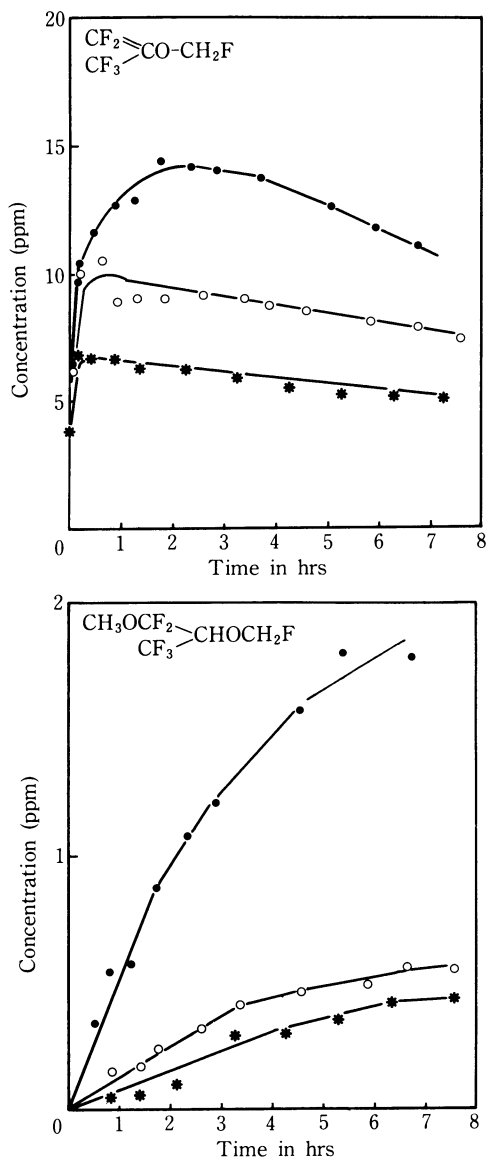


Fig. 6. Production of fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (p-1) and fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3) in the closed anesthetic circuit system with sodalime containing 2.7% of sevoflurane either fed with carbon dioxide or not.

- : The system was fed 200ml/min of carbon dioxide.
- * : The system was not fed carbon dioxide.
- : The system was added water instead of carbon dioxide.

ter reaction with methanol in the presence of sodium hydroxide. P-2, 3, 4, and 5 could be seen in the chromatogram.

DISCUSSION

Wallin⁸⁾ reported production of fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether and fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether by sodalime.

We identified five reaction products of sevoflurane with sodalime: fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (p-1) which is a dehydrofluorination product of sevoflurane and is also its impurity, fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3), fluoromethyl 2-methoxy-2,2-difluoro-1-(difluoromethylene)ethyl ether (p-2) and two isomers of fluoromethyl 2-methoxy-2-fluoro-1-(trifluoromethyl)vinyl ether (p-4 and 5) which are dehydrofluorination products of fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3).

Three reaction products have a methoxy radical in the molecules (Fig. 4). The reaction of sevoflurane with methanol in the presence of an alkali produces the same products (Fig. 9). These results suggest that sevoflurane reacts with sodalime and produces methanol. We considered the following mechanism for the production of methanol. Alkaline hydrolysis (nucleophilic) of halogenated alkyl is a well-known reaction⁴⁾. In our experimental system, hydrolysis of sevoflurane in the presence of sodalime that act as an alkali, cleaved the ether-bond to produced carboxylic acid and aldehyde. Methanol is produced by reaction of two aldehyde molecules (Cannizzaro's reaction).

This methanol appears likely to have reacted with dehydrofluorinated sevoflurane in the presence of an alkali to generate fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3), a methylation product. It is also possible that sevoflurane reacted with methanol in the presence of sodalime, since halogenated anesthetics are methylated by sodium methoxide⁷⁾. This methylation product is further dehydrofluorinated into three forms; p-2, 4, and 5.

Since the concentration of reaction products increased when distilled water was added, the increase in the products by addition of carbon dioxide is considered to be due to increase in water content, in addition to heat production of the reaction system secondary to the reaction between sodalime and carbon dioxide.

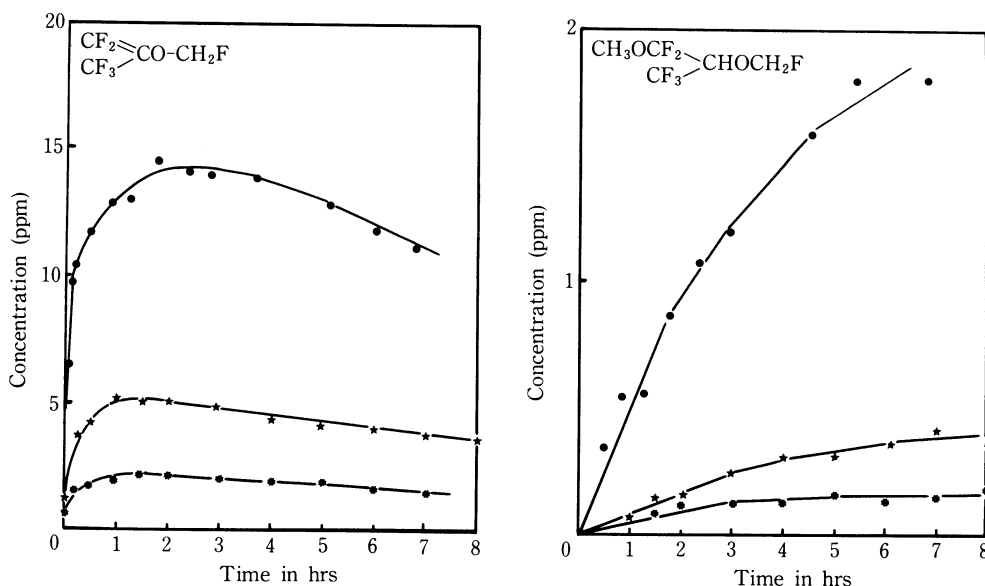


Fig. 7. Production of fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (p-1) and fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3) in the closed anesthetic circuit system in the different concentration of sevoflurane.

- : 0.6% of sevoflurane.
- ★ : 1.7% of sevoflurane.
- : 2.7% of sevoflurane.

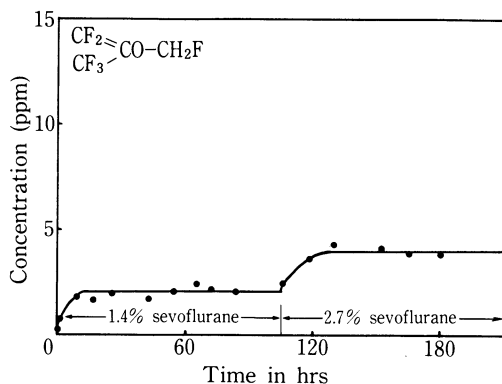


Fig. 8. Production of fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (p-1) in the semi-closed anesthetic circuit system either at 1.4% or 2.7% of sevoflurane. Fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3) was produced in a trace amount.

In the semi-closed anesthetic circuit with sodalime, fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (p-1) was detected at a maximum concentration of 4 ppm at 2.7% of sevoflurane, and fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3) was found only

in a trace amount. Sato⁶⁾, Central Research Laboratory, Maruishi Pharmaceutical Co., Ltd., informed that fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether (p-1) is weakly anesthetic with $AC_{50}=3.58\%$, $LC_{50}=10.17\%$ and $AI=2.84$.

We have concluded that sevoflurane can be used with sodalime in a semi-closed anesthetic circuit. In the closed anesthetic circuit, we have found in addition fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3) which has not yet been clarified its toxicity. We therefore recommend that sevoflurane be not used with sodalime in the closed anesthetic circuit until the toxicity of fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether (p-3) is clarified.

ACKNOWLEDGEMENT

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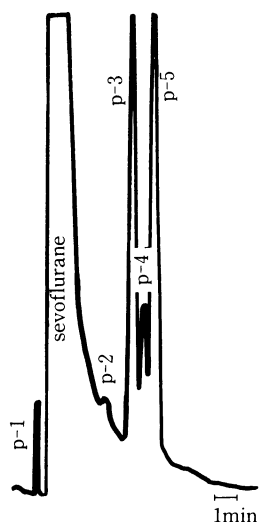


Fig. 9. Gas chromatogram of sevoflurane after reaction with methanol in the presence of an alkaline. Chromatogram shows 5 peaks excluding sevoflurane:

p-1: fluoromethyl 2,2-difluoro-1-(trifluoromethyl)vinyl ether, p-2: fluoromethyl 2-methoxy-2,2-difluoro-1-(difluoromethylene)ethyl ether, p-3: fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl)ethyl ether, p-4: fluoromethyl 2-methoxy-2-fluoro-1-(trifluoromethyl)vinyl ether, p-5: fluoromethyl 2-methoxy-2-fluoro-1-(trifluoromethyl)vinyl ether.

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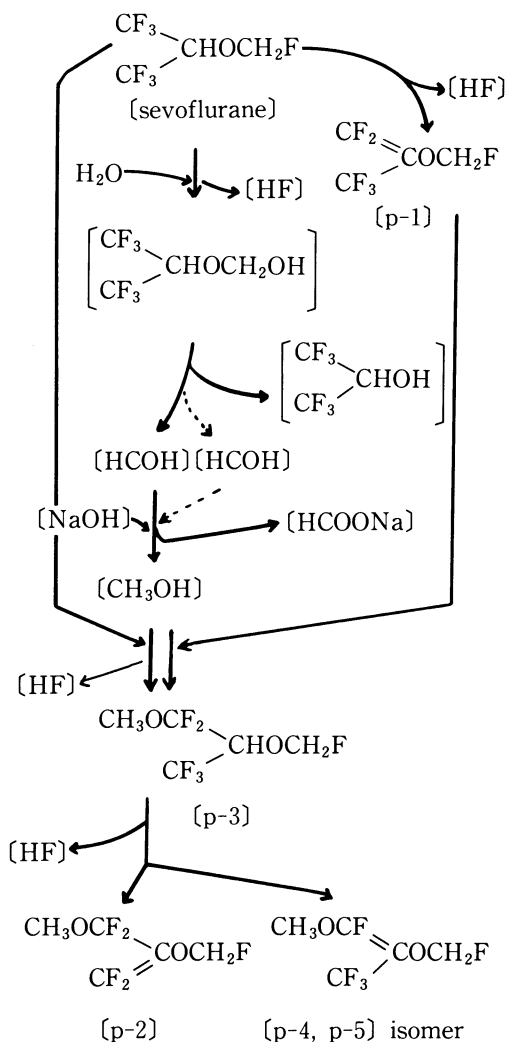


Fig. 10. Possible decomposition mechanism of sevoflurane by sodalime

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