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Decomposition of enflurane in soda lime

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Abstract: The stability of enflurane in soda lime was examined. A product of enflurane decomposition was detected after the reaction of enflurane with soda lime, but not in the absence of soda lime. The production of this compound, identified as 1-chloro-1,2-difluorovinyl difluoromethyl ether by gas chromatography-mass spectrometry, increased with time and temperature. The same decomposition product was produced by the reaction of enflurane with potassium, sodium, or calcium hydroxides, and it was also detected in the gas phase at a maximum concentration of 1.29 ppm at 420 min after 5% enflurane circulated with 200 ml/min carbon dioxide gas in a closed anesthesia circle system with a soda lime canister and a model lung. We concluded that enflurane was decomposed to 1-chloro-1,2-difluorovinyl difluoromethyl ether by soda lime.

Key words: Enflurane, Dehydrofluorination, Decomposition, Carbon dioxide absorber, Soda lime

Introduction

Enflurane (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether), a methyl ethyl ether containing fluoride, is a halogenated anesthetic which seems to be chemically stable. In clinical use, when enflurane is used in a semi-closed or closed anesthesia circle system, the patient re-inhales a part or all of the expired gas that has been passed through soda lime to absorb carbon dioxide. Because enflurane is usually used clinically with soda-lime, it is essential to ensure that this compound is stable in soda lime.

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Soda lime, used to absorb carbon dioxide, consists of potassium, sodium, and calcium hydroxides. Such volatile anesthetics as trichloroethylene, halothane, sevoflurane, and isoflurane are halogenated ethers and haloalkane which contain hydrogen and fluoride. They are decomposed by soda lime and hydrofluoride is eliminated from adjacent carbon atoms as follows. Trichloroethylene undergoes elimination to yield a toxic amount of dichloroacetylene [1]. Halothane also undergoes elimination to yield a small amount of difluorochlorobromoethylene, which is a toxic compound, and dehalogenation to produce trifluorochloroethane [2]. Sevoflurane is degraded into five compounds, four of which are the products of elimination: fluoromethyl 2,2-difluoro-1-(trifluoromethyl)-vinyl ether, fluoromethyl 2-methyl-2,2-difluoro-1-(difluoromethylene) ethyl ether, and two isomers of fluoro-methyl 2-methoxy-2-fluoro-1-(trifluoromethyl)-vinyl ether [3]. Isoflurane also undergoes elimination to produce 2,2-difluoro-1-chlorovinyl difluoromethyl ether [4].

Because enflurane contains both fluoride and hydrogen, it may react with soda lime to produce hydrofluoride. In view of the importance of the possible decomposition of enflurane by soda lime, we examined whether this occurred, with soda lime and with each of the bases, and tried to identify the products of this decomposition.

Materials and methods

Reagents

Wako lime (Katayama Chemical, Osaka, Japan) was used as soda lime. Analytical grade commercially available potassium, sodium and calcium hydroxides were used. Enflurane was obtained from Dainabot Pharmaceutical (Tokyo, Japan).

Degradation of enflurane by soda lime in a closed vessel

Soda lime (1.0 g) was placed in a 10-ml sealed vessel with enflurane (1.5 ml) at four different temperatures (40, 60, 100, and 140°C) each for 3 h. Aliquots were analyzed by gas chromatography-mass spectrometry. Potassium, sodium, or calcium hydroxide or silica (1.0 g) instead of soda lime were then reacted in the same vessel with the same volume of enfluane at 100°C for 3 h.

Closed anesthesia circle system with a model lung

An absorbent canister filled with 800 g of soda lime was placed in a closed anesthesia circle system using a 5-l rubber bag as a model lung. The system was then filled with 5% of enflurane in oxygen, and 200 ml/min of carbon dioxide was fed to the model lung. The mixed gas in the anesthesia circle system was circulated with a ventilator (Aika, Tokyo, Japan) for 7–7.5 h at a respiratory rate of 12 times/min and a tidal volume of 500 ml. Gaseous samples from the model lung were analyzed.

Gas chromatography—mass spectrometry

A Shimadzu GC-4A gas chromatograph was used which was equipped with a column (4 mm × 3 m) packed with dioctyl phthalate (DOP) and a flame ionization detector at 100°C. A helium carrier stream of 10 ml/min was used. We also used a Shimadzu GCMS-QP1000 mass spectrometer equipped with a 3 m column packed with DOP. The ion source temperature was set at 250°C and the ionizing energy at 70eV.

Results

A product was detected with a retention time of 2.0 min by gas chromatography in the reaction mixture containing enflurane and soda lime after 3 h. This compound was not detected in the absence of soda lime. The production of this compound increased with time (data not shown). The concentrations of this compound after 3 h reaction were trace at 40°C, 29.1 ppm at 60°C, 106 ppm at 100°C, and 912 ppm at 140°C.

The mass spectrogram of this compound has fragment ions at m/z 51 (CHF_2), 66 (CF_2O, CClF), 94 (CClFCO), and 97 (CClFCF) (Fig. 1).

The same compound was detected after the reaction of enflurane with potassium, sodium, or calcium hydroxide. This production rate was 21 ppm/3 h at 50°C and 14 800 ppm/3 h at 100°C by the reaction with potassium hydroxide, 3 ppm/3 h at 50°C and 1190 ppm/3 h at 100°C with sodium hydroxide, and trace amount at 50°C and 25 ppm/3 h at 100°C with calcium hydroxide. The reaction of enflurane with silica, which was present in soda lime as a binder, produced no compound.

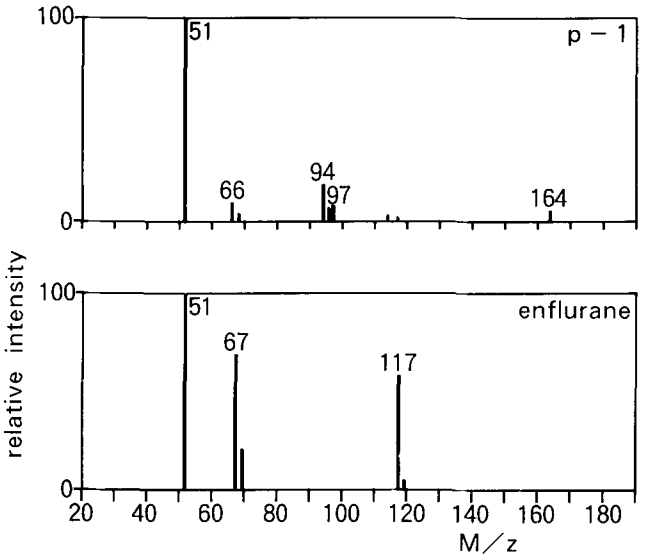

Fig. 1. Mass spectrogram of decomposition product of enflurane (top) and enflurane (bottom). We used a Shimadzu GCMS-QP1000 mass spectrometer equipped with a 3 m column packed with dioctyl phthalate (DOP). We set the ion source temperature at 250°C and ionizing energy at 70eV. m/z 51:$CCHF_2$, m/z 66:CF_2O or CClF, m/z 94:CClFCO, m/z 97:CClFCF, m/z 164:M (P-1), P-1:CClF = $CFOCHF_2$ enflurane: $CHClFCF_2OCHF_2$

The same compound was also detected in the gas phase of a closed anesthesia circle system containg a soda lime canister at 60 min after circulating 5% enflurane with carbon dioxide. This compound in the gas phase was increased to 420–450 min (the end of examinations). The maximum concentration was 1.29 ppm (Fig. 2).

Discussion

Enflurane, a fluorinated hydrocarbon, is adsorbed by soda lime as reported by Grodin et al. [5]. However, it is generally believed that enflurane does not react with soda lime and that it has no decomposition product [6]. Here we reacted enflurane with soda lime, and detected a decomposition compound. Since the compound was not detected without soda lime and the production of this compound increased with both time and temperature, it was obviously not an impurity or a product of a degradation due to the heat of the reaction but a product of the chemical reaction with enflurane. The mass spectrographic data indicated that this product was 1-chloro-1,2-difluorovinyl difluoromethyl ether. This was

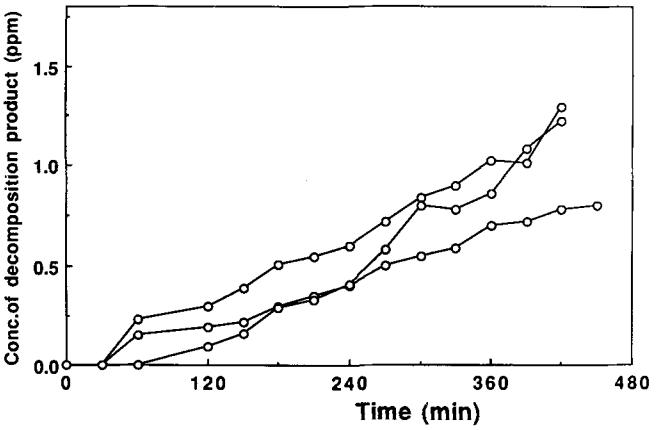

Fig. 2. Time course of the concentration of decomposition compound in closed anesthesia circle system over 8 h. The absorbent canister was filled with 800 g of soda lime which was placed in the closed anesthesia circle system with a 5–l rubber bag as a model lung. The circle system was filled with 5% of enflurane in oxygen, and 200 ml/min of carbon dioxide was fed to the model lung. The mixed gas in the anesthesia circle system was circulated with a ventilator (Aika) for 8 h at a respiratory rate of 12 breaths/min and a tidal volume of 500 ml. Gaseous samples from the model lung were analyzed. The compound was detectable after 60 min and increased to a maximum concentration of 1.29 ppm at 420 min

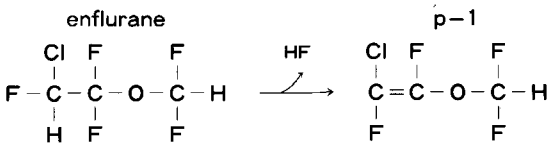

Fig. 3. Mechanism of decomposition of enflurane by soda lime

assumed to be produced by the dehydrofluorination of enflurane by potassium, sodium, and calcium hydroxides which constitute soda lime [Fig. 3]. Of these bases, potassium hydroxide showed the greatest effect on the decomposition of enflurane. These findings suggest that potassium hydroxide, which is contained in soda lime at a proportion of 2%–5% by weight, serves as an important activator in this reaction.

The formation of alkanes by the elimination of HX (X: halogen atom) from alkyl halides under ionic conditions is a well-known reaction. The mechanism by which hydrobromide is eliminated from enflurane may be as follows. In the initial phase, the base (hydroxide) is partially joined to the beta-hydrogen of the methyl group in the enflurane molecule, and a double bond begins to form between the two carbon atoms of the methyl group; the bromide atom is loosened from the attachment of the base to carbon, and the change is distributed between the attachment group and the bromide atom. In the terminal phase, the base separates from one carbon and bromide departs from the other, carrying with it a full negative charge.

In a closed anesthesia circle system with a carbon dioxide absorber and a model lung, the maximum decomposition product detected in the gas phase was 1.29 ppm when 5% enflurane was used, indicating that, when enflurane is used clinically it may also be decomposed by soda lime and the product inhaled by the patient. Since this compound contains a pi-electron in the molecule, it is possible that it may react with lipids, proteins, and/or nucleic acid. However, as its toxicity is unclear, further investigation is needed.

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