Synthesis of fluoro-dideutero-methyl 1,1,1,3,3,3-hexafluoro-2-propyl ether (deuterated sevoflurane)

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Summary

Sevoflurane was synthesized with deuterium substituents on the fluoromethoxy carbon. This was performed by a two-step reaction process that yielded deuterated sevoflurane of high purity.

Key words: sevoflurane, deuteration, fluorination

Introduction

Sevoflurane (fluoromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether) is a volatile anesthetic currently undergoing clinical trials for marketing in the United States (1,2). Its metabolism *in vivo* by the cytochrome P450 enzyme system results in the release of inorganic fluoride at rates sufficient enough that fluoride induced renal toxicity is a concern (2-4). Previously, it has been demonstrated that deuteration of the volatile anesthetics enflurane, halothane and methoxyflurane, markedly alters the metabolism of these compounds (5). For example, deuteration of halothane hinders its oxidative metabolism to trifluoroacetic acid, but not its reductive metabolism to release fluoride (5,6). Deuteration of methoxyflurane on the ß-ethyl carbon increases fluoride release upon metabolism, whereas deuteration of the ß-ethyl carbon of enflurane decreases fluoride liberation (5).

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Deuterium substitution for hydrogens on sevoflurane may also alter sevoflurane biotransformation and fluoride release from this anesthetic. Sevoflurane metabolism results in the formation of hexafluoro-2-propanol in addition to inorganic fluoride (7), therefore cytochrome P450 attack likely occurs on the fluoromethoxy carbon of sevoflurane. In order to determine the deuterium isotope effect on sevoflurane metabolism, it is necessary to synthesize sevoflurane deuterated on the fluoromethoxy carbon. The present study describes the synthesis of fluoro-dideutero-methyl 1,1,1,3,3,3-hexafluoro-2-propyl ether (D2-sevoflurane) using a two-step reaction process.

Materials and Methods

Chemicals. Hexafluoro-2-propanol (hexafluoroisopropanol, 99.5+%) and dimethyl-D_6-sulfate (99+%) were purchased from Janssen Chimica. Sevoflurane was obtained from PCR Chemicals, Inc. Bromine trifluoride (BrF_3) was supplied by Ozark-Mahoning, Inc. *(Caution - BrF_3 is a potent oxidizer that can burn all living tissue. It reacts vigorously with water and can react explosively with organic compounds. BrF_3 should only be used with proper protective equipment).*

D2-Sevoflurane synthesis. D2-Sevoflurane was synthesized by a modification of the method for the synthesis of sevoflurane described in U.S. patent 3,683,092 (8). Dimethyl-D_6-sulfate was reacted with hexafluoro-2-propanol to form trideuteromethyl hexafluoro-2-propyl ether. Trideuteromethyl hexafluoro-2-propyl ether was subsequently monofluorinated by reaction with BrF_3 (fig. 1).

Preparation of trideuteromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether. Hexafluoro-2-propanol (53.3 g) was added to 127 ml of 10% aqueous sodium hydroxide in a Pyrex flask. Dimethyl-D_6-sulfate (40

g) was added proportionwise during a 30 min period at 5°C while stirring. The reaction mixture was stirred for 2 hours at room

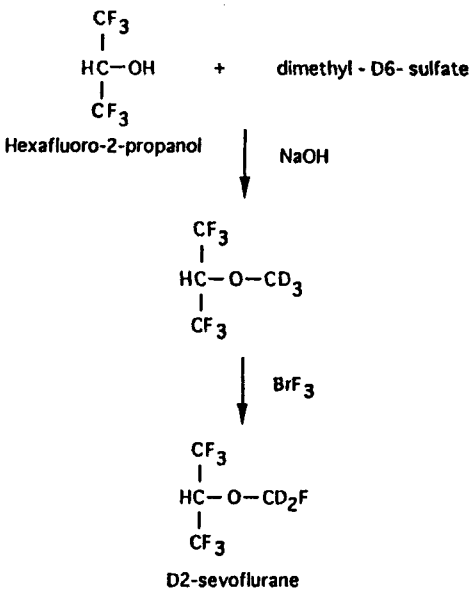

Figure 1 - Synthesis of D2-sevoflurane

temperature. Distillation of the reaction mixture yielded 45 g of trideuteromethyl hexafluoro-2-propyl ether.

Fluorination of trideuteromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether. Dried trideuteromethyl hexafluoro-2-propyl ether (8 ml) was placed in a round-bottom Pyrex flask fitted with a condenser. The flask was then placed in an ice-bath. BrF_3 (3 ml) was slowly added *via* teflon tubing over a 2 hour period while stirring. An exothermic reaction occurred. Following the addition of BrF_3, water was cautiously added to destroy excess BrF_3 in the reaction mixture. The reaction mixture was neutralized and washed successively with dilute sodium sulfite in water. The washed mixture was dried over anhydrous sodium sulfate and yielded 3.1 ml of product, a 39% yield. *Note - Hydrogen fluoride liberated during the addition of BrF_3 can dissolve pyrex glass if sufficient quantities are generated.*

Analysis of D2-sevoflurane. The product was analyzed by gas-chromatography (GC) using flame ionization detection. Samples were analyzed on a Supelcowax 10 capillary column (30m x 0.53 mm i.d., oven temp-100°C, helium carrier gas flow rate 17.5 ml/min) and on a column packed with 10% Igepal CO-880 15% UCON® LB-550X (1/8" i.d. x 20' stainless steel column; oven temp-105°C; helium carrier gas flow rate 24 ml/min). Mass-spectral analyses of the synthesized product were performed on a Nermag R10-10C mass spectrometer in the electron impact and chemical ionization modes. The mass spectrometer was equipped with a DB Wax 30 m x 0.2 mm x 0.5 µm capillary column for sample introduction.

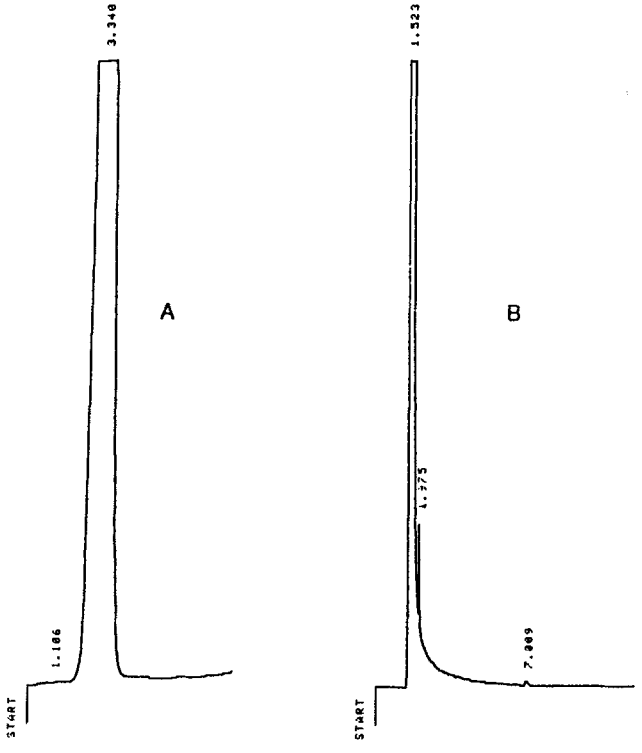

Figure 2 - Gas chromatograms of D2-sevoflurane on 10% Igepal CO-880 15% UCON® LB-550X (A) and Supelcowax 10 (B).

Results and Discussion

Gas chromatographic and mass-spectral analyses of the product generated as described above confirmed the synthesis of D2-sevoflurane at a purity of greater than 99%. The product chromatographed identically with sevoflurane using both gas-chromatographic procedures (fig. 2). Gas chromatography of the product on Supelcowax 10, which resolves hexafluoro-2-propanol (retention time - 7.0 min) from sevoflurane (1.5 min), showed that only trace amounts of hexafluoro-2-propanol (0.032%) and a minor

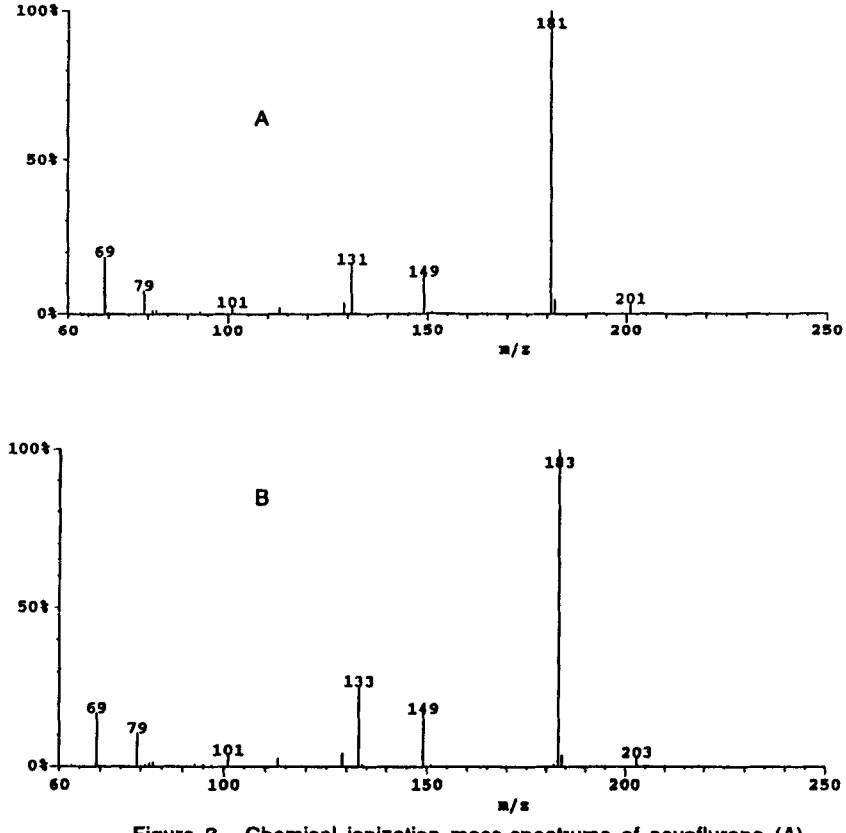

Figure 3 - Chemical ionization mass-spectrums of sevoflurane (A) and D2-sevoflurane (B).

contaminant (0.1%) were present. Chromatography of the product on 10% Igepal CO-880 15% UCON® LB-550X, which separates

sevoflurane or D2-sevoflurane (retention time - 3.3 min) from methyl- or trideutero-methyl hexafluoro-2-propyl ether (2.2 min), showed that no detectable amounts of trideutero-methyl hexafluoro-2-propyl ether contaminated the product.

Gas chromatographic/mass-spectral analyses of sevoflurane and the product using the chemical ionization mode with methane gas are shown in fig. 3. Sevoflurane analysis resulted in an M+1 ion of *m/z* 201, whereas the product showed an M+1 ion of two mass units greater, *m/z* 203. The most abundant ion fragment occurred at *m/z* 181 for sevoflurane (loss of F), and at 183 for the product. The *m/z* 131 fragment from sevoflurane, representing loss of CF_3, was the next most abundant ion. The product showed this ion fragment at *m/z* 133. The relative abundance of the ion fragments to each other where similar between sevoflurane and the product. Electron impact mass-spectral analysis revealed the fragment ions *m/z* 181 and 131 for sevoflurane, and *m/z* 183 and 133 for the product (not shown). No parent ion of either compound was observed by electron impact mass spectral analysis. These GC/MS data confirm that fluoro-dideutero-methyl 1,1,1,3,3,3-hexafluoro-2-propyl ether was the product, and that there was no detectable sevoflurane or monodeuterated sevoflurane contamination.

The reaction of hexafluoro-2-propanol with dimethyl-D_6-sulfate to form trideuteromethyl hexafluoro-2-propyl ether is one that generates a high yield. The calculated yield of 85% is typical. On the other hand, several factors were found to significantly affect the yield of D2-sevoflurane from the reaction of BrF_3 with trideuteromethyl hexafluoro-2-propyl ether. Rapid rates of introduction of BrF_3 into the reaction mixture results in a vigorous reaction generating excess heat and gas. In addition to an uncontrollable reaction, rapid BrF_3 addition increases loss of both the starting material and product by volatilization. This is a

particular problem for small scale reactions such as that used here and is a large factor in reducing the yield of the fluorination reaction. Also, if the reaction is not carried to completion, that is, if insufficient BrF_3 is added to completely react with the trideuteromethyl hexafluoro-2-propyl ether present, trideuteromethyl hexafluoro-2-propyl ether will be recovered with the product.

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