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Journal of Fluorine Chemistry 71 (1995) 55–58

JOURNAL OF FLUORINE CHEMISTRY

Fluoro-dideutero-methyl 1,1,1,3,3,3-hexafluoroisopropyl ether (D_2-sevoflurane) reactions on soda lime: deuterium content of deuterated sevoflurane and its volatile degradation products

Jan A. Ruzicka, Max T. Baker *

Department of Anesthesia, University of Iowa, Iowa City, IA 52242, USA

Received 29 December 1993; accepted 19 April 1994

Abstract

The degradation of the experimental anesthetic, fluoro-dideutero-methyl 1,1,1,3,3,3-hexafluoroisopropyl ether (D_2-sevoflurane) on soda lime (Sodasorb®) has been compared with sevoflurane and examined in regard to product deuterium content. Similar products and rates of degradation were found between sevoflurane and D_2-sevoflurane, and all D_2-sevoflurane products contained the fluorodideuteromethoxy group. Four products contained a trideuteromethoxy moiety, indicating the addition of methanol derived from the fluoromethoxy carbon of D_2-sevoflurane.

Keywords: Sevoflurane; D_2-Sevoflurane; Deuteration; Soda lime; Degradation products

1. Introduction

Sevoflurane ($CF_3CH(CF_3)OCH_2F$) is an inhalational anesthetic currently undergoing clinical trials in the United States. This anesthetic possesses clinically desirable properties including a low pungency, and a low blood:gas solubility coefficient (0.61) which allows rapid induction and recovery from anesthesia [1]. Two major concerns with its use exist, however. In vivo, sevoflurane undergoes cytochrome P_{450}-mediated hydroxylation on the fluoromethoxy carbon to release relatively high amounts of inorganic fluoride. In a number of patients, plasma fluoride levels considered potentially nephrotoxic (>50 μM) have been achieved [2,3]. Secondly, in commonly used rebreathing circuits a small fraction of the sevoflurane molecules are degraded when they contact the basic CO_2 absorbers, such as soda lime or Baralyme, to release volatile compounds in the circuit. The major product released is $CF_2{=}C(CF_3)OCH_2F$ (compound A) which results from the dehydrofluorination of sevoflurane, and $CH_3OCF_2CH(CF_3)OCH_2F$ (compound B) which results from the addition of methanol to compound A is formed in lesser amounts [4–6]. Other products are usually not detectable in typical anesthesia circuits; however, dehydrofluorination products of compound B, the *E*- and *Z*-isomers of $CH_3OCF{=}C(CF_3)OCH_2F$ (compounds C and D) and $CH_3OCF_2C(=CF_2)OCH_2F$ (compound E), are formed upon reaction of sevoflurane with soda lime at elevated temperatures [6–8]. In addition to high fluoride release, the metabolism and toxicities of these products are major points of uncertainty with regard to the safety of sevoflurane administration to humans [9,10].

As an experimental anesthetic, we have synthesized a derivative of sevoflurane in which the two fluoromethoxy hydrogens of sevoflurane were substituted with deuteriums ($CF_3CH(CF_3)OCD_2F$, D_2-sevoflurane) [11]. This compound exhibits anesthetic properties similar to sevoflurane, but is metabolized to such a low degree that fluoride release at nephrotoxic levels is not a concern [12]. Rates of degradation of this compound on soda lime are not expected to differ from sevoflurane; however, potential detrimental effects of the products may be altered because of their deuterium content and thus isotope effects on their in vivo metabolism [13]. The deuterium content of D_2-sevoflurane and its degradation products following their interaction with soda lime is not known, and not clearly predictable because of possible deuterium–hydrogen exchange mechanisms and the fact that the proposed mechanism of methanol formation from sevoflurane has not been confirmed [6]. The present study compared the degradation of D_2-sevoflurane and sevoflurane on the most commonly used CO_2 absorber in anesthesia circuits, i.e. soda lime.

* Corresponding author.

SSDI 0022-1139(94)03152-5

The deuterium content of the products was determined by gas chromatographic/mass spectrometry and product formation evaluated in view of the proposed mechanisms of sevoflurane degradation.

2. Experimental details

Sevoflurane was a gift from Abbott Laboratories (Abbott Park, IL). D_2-sevoflurane was prepared from hexafluoro-2-propanol and dimethyl-d_6-sulfate as described [11]. Soda lime (Sodasorb®, 79% $Ca(OH)_2$, 1.2% NaOH, 2.3% KOH, 0.4% SiO_2, 13.6% H_2O) was obtained from W.R. Grace (Atlanta, GA).

For the determination of sevoflurane and D_2-sevoflurane degradation products, fresh soda lime (0.5 g) was placed in 10 ml hypovials which were sealed and evacuated. Into each vial was injected either sevoflurane or D_2-sevoflurane (0.3 mmol), and the pressure within the vials was restored to atmospheric using a syringe. The vials were heated at 120 °C for 40 min or 45 °C up to 5 h. After cooling to room temperature, samples of headspace gas (100 μl) were withdrawn by gas-tight syringe and analyzed by gas chromatography.

Gas chromatographic analyses of sevoflurane, D_2-sevoflurane, and their respective degradation products were performed with a Hewlett Packard 5890 series II gas chromatograph equipped with an FID detector and an Alltech AT-624 cyanopropylphenyl dimethoxypolysiloxane column (30 m×0.53 mm i.d.). The oven was operated isocratically at 35 °C and helium (17 ml min^{-1}) served as the carrier gas.

Mass spectral analyses were performed using a Nermag R10-10C mass spectrometer operated in the electron impact mode. Samples were introduced using the Alltech AT-624 column.

3. Results

Gas chromatographic/mass spectral analysis of sevoflurane and D_2-sevoflurane confirmed the identity and isotopic purity of these two starting materials [11]. For sevoflurane, key fragments included (EI) *m/z*: 199 (M^+-H); 181 (M^+-F); 151 ($(CF_3)_2CH$); 131 (M^+-CF_3, base peak); 79 ($CF_2C(O)H$); and 69 (CF_3). For D_2-sevoflurane, the analogous peaks were *m/z*: 200 (M^+-D); 183 (M^+-F); 151 ($(CF_3)_2CH$); 133 (M^+-CF_3, base peak); 79 ($CF_2C(O)H$); and 69 (CF_3). The appearance of *m/z* 200 as the highest mass ion from D_2-sevoflurane (mol wt. 202) implies a similar loss from sevoflurane of a fluoromethyl hydrogen, and not the isopropyl hydrogen, to give the *m/z* 199 fragment.

Heating of the vials (120 °C for 40 min) containing soda lime and either sevoflurane or D_2-sevoflurane resulted in five volatile products and recoverable quantities of sevoflurane or D_2-sevoflurane as revealed by gas chromatographic analysis (Fig. 1). The nearly identical product profiles show that both forms of sevoflurane are degraded to the same products and product ratios as determined by GC analysis. At 45 °C, the approximate soda lime temperature attained in anesthesia circuits [4–6], the degradation rates and products of D_2-sevoflurane in the sealed vessels were also similar to those of sevoflurane (data not shown). Sevoflurane containing vials not heated or not containing soda lime showed no product formation.

GC/MS analysis of recovered sevoflurane and D_2-sevoflurane following heating with soda lime revealed identical mass spectra as the original compounds described above. Analysis of the sevoflurane and D_2-sevoflurane decomposition products by GC/MS yielded the following principal fragment ions. Identified products are listed in their order of elution, with fragments given for sevoflurane (H_2) and D_2-sevoflurane (D_2).

Compound A: (H_2) *m/z*: 180 (M^+); 161 (M^+-F); 128 ($F_2CC(O)CF_2$); 78 (F_2CCO); 69 (CF_3, base peak). (D_2) *m/z*: 182 (M^+); 163 (M^+-F); 128 ($F_2CC(O)CF_2$); 78 (F_2CCO); 69 (CF_3, base peak).

Compound E: (H_2) *m/z*: 192 (M^+); 161 (M^+-CH_3O); 159 (M^+-CH_2F); 140 ($CH_3OCFC(O)CF_2$); 111 ($M^+-CH_3OCF_2$); 97 (CF_3CO); 81 ($M^+-CF_2COCH_2F$); 69 (CF_3, base peak). (D_2) *m/z*: 197 (M^+); 163 (M^+-CD_3O); 162 (M^+-CH_2F); 143 ($CD_3OCFC(O)CF_2$); 113 ($M^+-CD_3OCF_2$); 97 (CF_3CO); 81 ($M^+-CF_2COCH_2F$); 69 (CF_3, base peak).

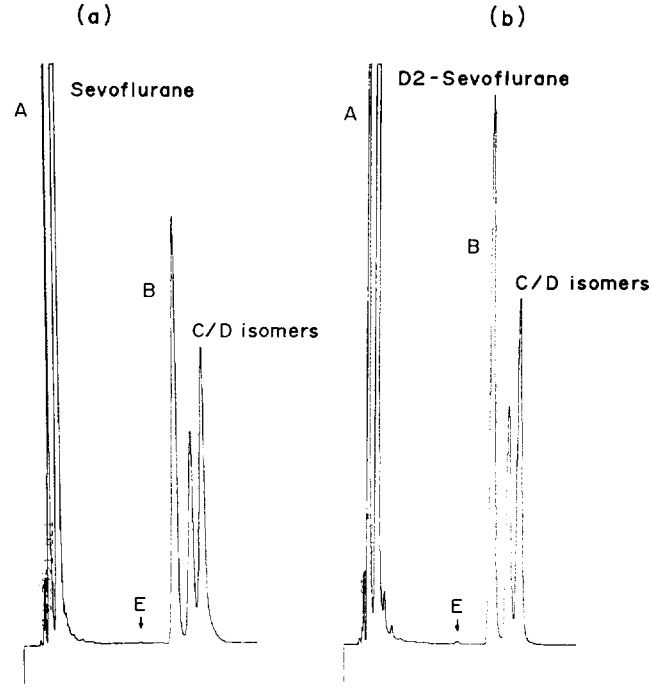

Fig. 1. Gas chromatographs of the soda lime-dependent degradation products of sevoflurane (A) and D_2-sevoflurane (B).

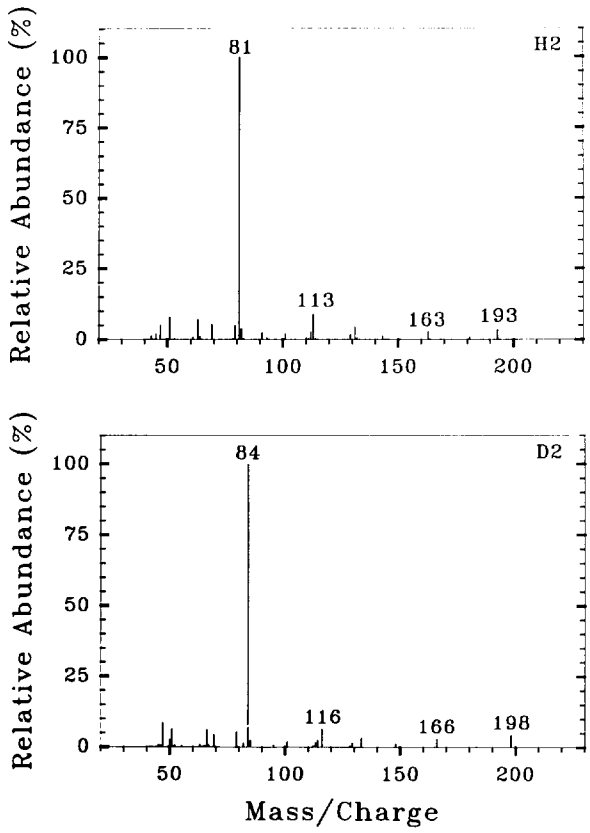

Fig. 2. Mass spectra for compound B from sevoflurane (top) and D_2-sevoflurane (bottom).

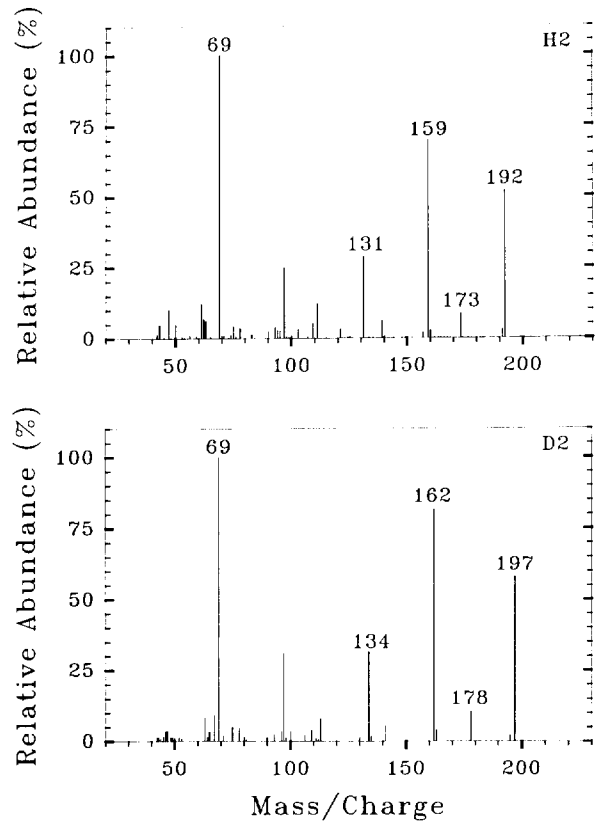

Fig. 3. Mass spectra for compounds C/D from sevoflurane (top) and D_2-sevoflurane (bottom).

Compound B: (H_2) *m/z*: 193 ($M^+ - F$); 163 ($CH_3OCF_2CHCF_3$); 113; 81 (CH_3OCF_2, base peak). (D_2) *m/z*: 198 ($M^+ - F$); 166 ($CD_3OCF_2CHCF_3$); 116; 84 (CD_3OCF_2, base peak) (Fig. 2).

Compounds C and D: (H_2) *m/z*: 192 (M^+); 173 ($M^+ - F$); 159 ($M^+ - CH_2F$); 131 ($CH_2FOCHCF_3$); 69 (CF_3, base peak). (D_2) *m/z*: 197 (M^+); 178 ($M^+ - F$); 162 ($M^+ - CD_2F$); 134 ($CD_2FOCDCF_3$); 69 (CF_3, base peak) (Fig. 3). Since they are geometric isomers of $CH_3OCF{=}C(CF_3)OCH_2F$, compounds C and D had indistinguishable mass spectral profiles. Their order of elution was not determined.

4. Discussion

Upon interaction of D_2-sevoflurane with soda lime at elevated temperatures, no evidence of deuterium–hydrogen isotope exchange on D_2-sevoflurane was found. Loss of one or both deuterium via exchange would be expected to yield a peak at *m/z* 199 as seen with sevoflurane, yet no such peak was observed.

Except for their deuterium content, the products of D_2-sevoflurane were structurally identical to those formed upon the base-catalyzed degradation of sevoflurane, i.e. compounds A–E (Fig. 4) [6–8]. The first volatile product formed, compound A, arises from the

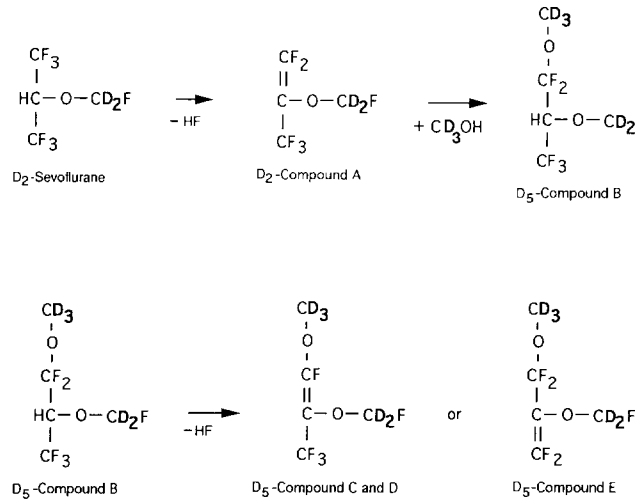

Fig. 4. Pathways for the formation of the deuterated degradation products of D_2-sevoflurane.

base-induced elimination of hydrogen fluoride to form the difluorinated olefin. Addition of methanol to this olefin gives the diether compound B. Loss of hydrogen fluoride from compound B yields one of the three olefins, compounds C, D or E. Each of the compounds B–E from D_2-sevoflurane produced molecular ions of five mass units greater than those from sevoflurane, showing that trideuterated methanol is the moiety added

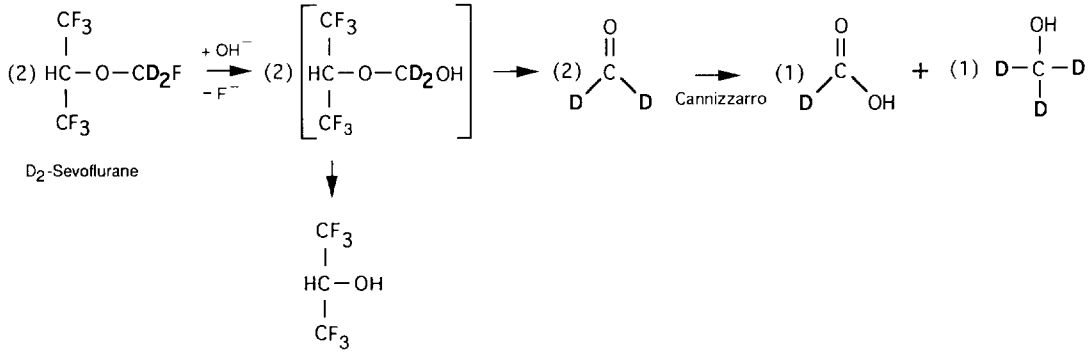

Fig. 5. Pathway for the formation of D_3-methanol from D_2-sevoflurane.

to compound A. The ion of *m/z* 81 (CH_3OCF_2) relative to that of *m/z* 84 (CD_3OCF_2) from the forms of compound B generated from sevoflurane and D_2-sevoflurane, respectively, and the ion of *m/z* 159 ($M^+ - CH_2F$) relative to that of *m/z* 162 ($M^+ - CD_2F$) from compounds C and D generated from sevoflurane and D_2-sevoflurane, confirm the trideuteromethoxy moieties. The deuterium purity of the trideuteromethoxy groups and fluorodideuteromethoxy groups of all products indicated no significant deuterium–hydrogen exchange following their formation.

The presence of the trideuteromethoxy groups on compounds B–E from D_2-sevoflurane demonstrates that methanol is derived from the fluorodideuteromethoxy group of D_2-sevoflurane. Methanol may be formed from the formaldehyde released by nucleophilic displacement of the fluoromethoxy fluoride substituent by hydroxide [14]. Two formaldehyde molecules may then undergo a Cannizzaro reaction to form methanol. A pivotal mechanistic feature of the Cannizzaro reaction involves the reduction of one aldehyde molecule by another in base via a hydride shift, producing the corresponding carboxylic acid and alcohol [15]. One trideuteromethanol molecule can consequently arise from the interaction of two CD_2O molecules by way of a deuteride shift (Fig. 5). Our data confirm the proposal by Hanaki et al. [6] that methanol from sevoflurane on soda lime originates from formaldehyde. While the fluoromethoxy carbon of sevoflurane serves as the ultimate source of the methanol carbon as formaldehyde, one or more dideuterofluoromethoxy-containing breakdown products may also directly release CD_2O upon reaction with soda lime.

In summary, the breakdown products potentially inhaled by patients administered the experimental anesthetic D_2-sevoflurane will be similar in structure and quantity to those liberated from sevoflurane. However, because of their deuterium content, particularly compounds B–E which contain five deuteriums, it is possible that the degradation products will be subject to large deuterium isotope effects on their metabolism. Clarification of their metabolic and toxicological properties is warranted.

Acknowledgement

The authors thank Chu Han Li and Dennis M. Charkowski for performing the GC/mass spectral analyses.

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