Deuterium Labeling of Methyl 1,1,1,3,3,3-Hexafluoroisopropyl Ether

Max T. Baker, William C. Ronnenberg, Jan A. Ruzicka*, and John H. Tinker. Department of Anesthesia, University of Iowa, Iowa City, IA 52242. Phone: (319) 335-6585, FAX (319) 353-5590. Email: Bakerm@anesthesia-po.anesth.uiowa.edu.

Summary

Trideuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether was synthesized by the reductive dechlorination of trichloromethyl 1,1,1,3,3,3-hexafluoro-isopropyl ether. This reaction was performed by zinc/zinc chloride catalyzed reduction in acetic acid-D. This reaction yielded 80% methyl 1,1,1,3,3,3-hexafluoroisopropyl ether consisting of approximately 70% trideuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether and 26% dideuteromethyl 1,1,1,3,3,3-hexafluoro-isopropyl ether.

Key words: Deuterium, Methyl hexafluoroisopropyl ether, Acetic acid-D, Deuteration, and Dechlorination

Introduction

The metabolism of the fluorinated anesthetics is associated with the liver and kidney toxicities induced by exposure to these compounds (1,2). Deuteration of the anesthetics, halothane, methoxyflurane and enflurane, has yielded compounds more resistant to metabolism than their nondeuterated analogues while they retained their anesthetic properties (3). As a consequence, deuterated anesthetics are thought to be useful anesthetics less likely to produce toxic side effects.

We demonstrated that deuteration of the anesthetic sevoflurane, fluoromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether, on its fluoromethoxy group, resulted in a compound the metabolism of which is reduced 70-90% in rat liver microsomes and whole rats (4). Synthesis of fluoro-dideutero methyl 1,1,1,3,3,3-hexafluoroisopropyl ether (deuterated sevoflurane) was previously accomplished by the methylation of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) with dimethyl-D_6-sulfate, followed by treatment of the trideuteromethyl ether with bromine trifluoride for the

*Present address: Department of Chemistry, North Georgia College, Dahlonega, GA 30533.

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single fluorine addition (5). A disadvantage of this procedure, as well as others that entail addition of a trideuterated methyl group to HFIP, is the requirement for relatively expensive deuterated starting materials such as dimethyl-D_6-sulfate, D_3-methyl iodide, or D_3-methyl bromide.

The synthesis of deuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ethers using deuterium from less expensive materials would represent a more economical step in the production of deuterated sevoflurane. A possible process for this is direct deuterium replacements on the methyl group of methyl 1,1,1,3,3,3-hexafluoroisopropyl ether using deuterium from easily prepared deuterium donating solvents. The most common procedure for this is base-catalyzed deuterium-hydrogen exchange in D_2O (3). This method, however, is not useful for methyl or fluoromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether deuteration because of the susceptibility of the hexafluoroisopropyl moieties to base-catalyzed hydrogen fluoride elimination (6). An alternate route is the reductive dehalogenation of a halogenated analogue of the compound of interest in acetic acid-D or D_2O. This method has been used in the synthesis of D-camphor (7), D-coumarin (8) and D-pyridines (9). Such labeling in general is restricted in application because the halogens must be specificly placed at the positions to be labeled and they must be selectively removed rendering the desired deuterated compound.

Due to the fact that trichloromethyl 1,1,1,3,3,3-hexafluoropropyl ether can be easily produced in high yield (10), we evaluated the reductive dechlorination of this compound as a means of synthesizing deuterated methyl 1,1,1,3,3,3-hexafluoroisopropyl ether. We report the formation of trideuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether by a simple zinc-catalyzed reduction of trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether in acetic acid-D.

Methods

Chemicals. Hexafluoroisopropanol was purchased from Hoechst AG (Frankfurt). Dimethyl sulfate, acetic anhydride, sodium methoxide, zinc dust, and D_2O (99.5% D) were from Aldrich chemicals (St Louis, MO).

Instrumentation. Gas chromatography was performed using a Hewlett-Packard 5890 gas chromatograph equipped with a flame ionization detector and an Alltech AT-624 5% cyanopropyl-polysiloxane column (30 m x 0.53 mm id). The injector, oven, and detector temperatures were 250, 35 and 260°C, respectively. Helium (17 ml/min) served as the carrier gas. GC/MS data was

acquired using a Trio-1 mass spectrometer with data analysis using Lab-Base software. A J&W Scientific BD-1 column (15 m x 0.23 mm id) was used for sample introduction.

Trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether synthesis. Methyl 1,1,1,3,3,3-hexafluoroisopropyl ether was prepared by the methylation of hexafluoroisopropanol using dimethyl sulfate as previously described (11,4). Trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether was synthesized essentially as reported by Speers *et al* (10). In brief, methyl 1,1,1,3,3,3-hexafluoroisopropyl ether (35 ml) was placed in a 50 ml flask fitted with a dewar/dry ice condenser. Chlorine (Cl_2) was slowly bubbled into the solution which was illuminated with a 300 watt incandescent lamp. Chlorine was continuously introduced into the solution until trichlorination was complete. The reaction was monitored for the formation of trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether and the depletion of methyl 1,1,1,3,3,3-hexafluoroisopropyl ether by gas chromatographic analysis. Following the chlorination process, the trichlorinated ether was treated with dilute sodium hydroxide, washed three times with distilled water, dried with phosphorous pentoxide, and distilled.

Trideuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether synthesis. Reductive deuterium labeling was performed in a 250 ml sidearm flask connected to a 50 ml cold-trap chilled with dry ice. Seventy five milliliters of acetic acid-D (CH_3COOD) was placed in the flask at room temperature followed by the addition of 9.0 g sodium methoxide. Twenty five grams of zinc dust and 5.0 g of dry $ZnCl_2$ were added to the solution which was stirred vigorously with a magnetic stirrer. The mixture was heated to 80°C. Ten milliliters of trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether (16.2 g) were added over a 15 min period. A reaction occurred with a noticeable evolution of vapor. The temperature of the reaction mixture was then raised to 100°C for 30 min. Product collection in the cold trap was facilitated by slowly purging the head space of the reaction mixture with helium. The contents of the trap were assayed by GC for methyl hexafluoroisopropyl ether and trichloromethyl hexafluoroisopropyl ether.

Acetic acid -D (CH_3COOD). Acetic acid-D was prepared in a manner similar to that previously described (12). Acetic anhydride (1.06 mol, 100 ml) was placed in a flask fitted with a water-cooled condenser. The acetic anhydride was heated to 100-110°C and stirred. Twenty milliliters of D_2O (1.10 mol, 99.9% D) was slowly added to the acetic anhydride. The mixture was allowed to stir for an additional 2 hours between 100 and 110°C. Complete conversion of acetic

anhydride to acetic acid was verified by gas chromatography. Excess D_2O was removed by boiling the acetic acid-D (118°C) an additional 10 minutes.

Results and Discussion

Using the method of Speers *et al* (10), methyl 1,1,1,3,3,3-hexafluoroisopropyl ether was essentially completely converted to trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether by photochlorination (figure 1). Chloromethyl- and dichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ethers were formed and then depleted from the reaction mixture as the chlorination process proceeded. This indicated stepwise additions of chlorine to the methyl group. Confirmation of trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether as the end chlorinated product was by GC-mass spectral analysis. The following major fragment ions were observed: m/z 249,251,253 (M^+-Cl); 151 ($CF_3CHCF_3^+$), 167 ($CF_3CHOCF_3^+$), 69 (CF_3^+). No trichloromethyl 1,1,1,3,3,3-hexafluoro-2-chloro-propyl ether was formed under these chlorinating conditions.

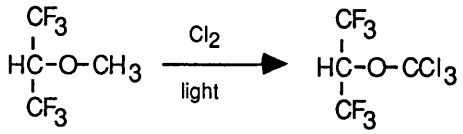

Figure 1. Photochlorination of methyl 1,1,1,3,3,3-hexafluoroisopropyl ether.

The reaction of trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether with zinc dust in acetic acid-D:sodium methoxide resulted in the formation of trideuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether as the major product (figure 2). Following the addition of 10 ml trichloromethyl ether to the reaction mixture, 7.2 ml of product was recovered in the cold trap. Analysis of this product by GC revealed a major product that chromatographed identically with methyl 1,1,1,3,3,3-hexafluoroisopropyl ether. The contents were assayed using authentic methyl hexafluoroisopropyl ether, d = 1.36, (13) and trichloromethyl hexafluoroisopropyl ether (d =

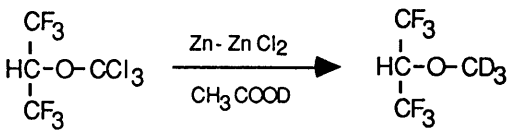

Figure 2. Reductive dechlorination of trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether.

1.62, estimated in this study) as standards. The deuterated methyl ether was estimated to be present in 80% purity. Including the presence of 12% trichloromethyl ether, there was a 92% recovery of the starting material as the trichloromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether and as deuterated methyl 1,1,1,3,3,3-hexafluoroisopropyl ether.

The identity of the product as predominantly trideuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether was confirmed by comparison of its mass spectral fragmentation pattern with that of methyl 1,1,1,3,3,3-hexafluoroisopropyl ether (Figure 3). Mass spectral analysis of authentic methyl 1,1,1,3,3,3-hexafluoroisopropyl ether ($(CF_3)_2CHOCH_3$) showed ions of (e/z) 182

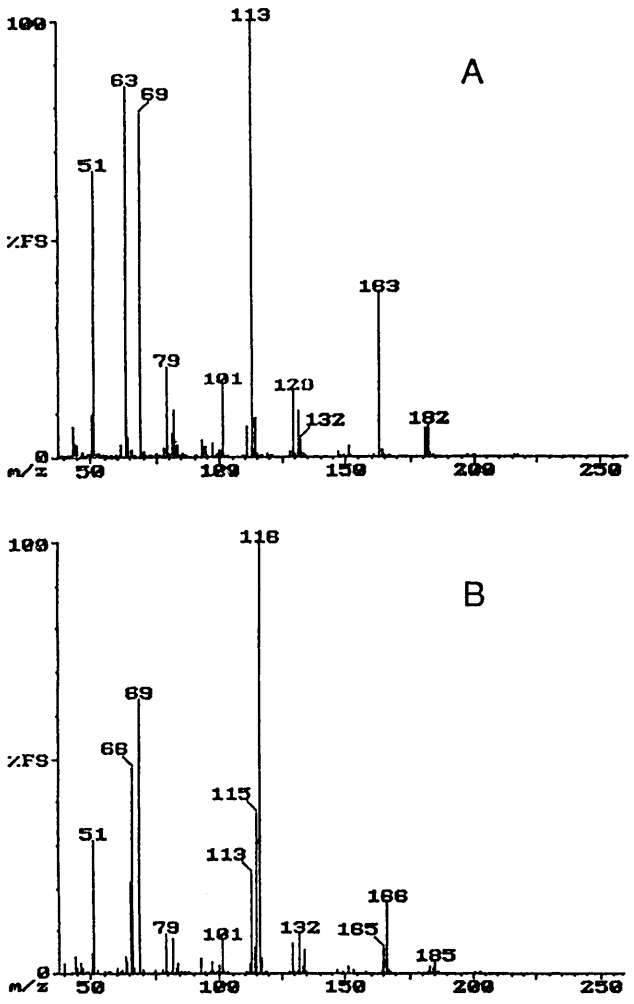

Figure 3. Mass spectra of methyl 1,1,1,3,3,3-hexafluoroisopropyl ether (A) and deuterated methyl 1,1,1,3,3,3-hexafluoromethyl ether products (B).

(M^+), 181 (M^+ - H), 163 (M^+ - F), 113 (M^+ - CF_3), 69 (CF_3^+). Mass spectral analysis of the product showed the corresponding ions, 185 (M^+), 183 (M^+ - D), 166 (M^+ - F), 116 (M^+ - CF_3), and 69 (CF_3^+) thus confirming $(CF_3)_2CHOCD_3$ as the major compound present. Accompanying ions in lesser amounts were (e/z) 184 (M^+ -D), 165 (M^+ -F), and 115 (M^+ -CF_3) indicating the presence of $(CF_3)_2CHOCD_2H$. The relative abundances of the major fragment ion containing the methoxy moiety (116 *vs* 115 and 114) showed that the deuterated product consisted of approximately 70% $(CF_3)_2CHOCD_3$, 26% $(CF_3)_2CHOCD_2H$, and less than 4% $(CF_3)_2CHOCDH_2$ for a total methoxy deuterium content of 88.5% .

In the development of this process, it was determined that a nearly anhydrous solvent system provided the best yield of trideuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether. A significant amount of D_2O in the reaction mixture resulted in the formation of hexafluoroisopropanol, possibly a result of the hydrolysis of reductive chlorinated intermediates. The mechanism of deuterium addition to the molecule is presumably due to the formation of methoxy carbon-centered free-radicals *via* reductive dechlorination followed by abstraction of deuteriums from acetic acid-D. While the reduction may involve step-wise dechlorinations, only small quantities of chloro- and dichloromethyl intermediates were observed in the reductive conditions used indicating that trichloromethyl ether readily dechlorinated to trideuteromethyl ether.

In summary, this report demonstrates that methyl 1,1,1,3,3,3-hexafluoroisopropyl ether can be deuterated on the methyl group in high yield and deuterium purity by simple photochlorination, followed by zinc-catalyzed reduction in acetic acid-D. The deuterated methyl ether can be further purified by conventional distillation and used for the synthesis of fluorodideuteromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether (4).

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