

Sevoflurane Breakdown Produces Flammable Concentrations of Hydrogen

Marshall B. Dunning III, Ph.D.,* Lynn E. Bretscher, Ph.D.,† Shahbaz R. Arain, M.D.,‡ Yanina Symkowski, M.D.,§ Harvey J. Woehlck, M.D.||

Background: Fires, explosions, and extreme heat production may occur when sevoflurane reacts with desiccated barium hydroxide lime. The identity of the flammable gas has not previously been published, although carbon monoxide, methanol, formaldehyde, and methyl formate have been identified in low quantities.

Methods: The authors reacted sevoflurane with excess desiccated barium hydroxide lime or soda lime at 55°, 100°, 200°, 300°, and 400°C. Formaldehyde, methanol, sodium formate, and hexafluoroisopropanol were reacted with barium hydroxide lime at 300° or 400°C. The authors measured hydrogen production by gas chromatography with a thermal conductivity detector and calculated the molar yield of hydrogen produced.

Results: Up to 3 moles of hydrogen were produced per mole of sevoflurane degraded. Each mole of formaldehyde produced up to 2 moles of hydrogen at 400°C. Formate and hexafluoroisopropanol produced up to 1 mole of hydrogen each at 400°C. More than 2 moles of hydrogen were produced by methanol at 400°C. Soda lime and barium hydroxide lime produced similar amounts of hydrogen from sevoflurane above 200°C, but barium hydroxide lime produced more than soda lime at lower temperatures. The temperature above which large amounts of hydrogen were produced seemed to be 300°C.

Conclusions: Up to 3 moles of hydrogen are produced by the chemical reaction of sevoflurane with heated, desiccated absorbent. The high yield, ease of ignition, and low tissue solubility of hydrogen make it the most likely fuel in anesthesia machine fires due to the reaction of sevoflurane with desiccated absorbent.

FIREs, explosions, and extreme heat production may occur when sevoflurane breaks down in association with desiccated barium hydroxide lime.¹⁻⁵ The identity of the flammable gas has not been reported. In anesthesia circuits, carbon monoxide has been identified at up to 11,000 ppm (1.1%) during the reaction of sevoflurane with desiccated barium hydroxide lime just before spontaneous combustion.¹ The flammable limits of carbon monoxide in air are 12-74%,⁶ making 1.1% far below the lower flammable limit. Sevoflurane is not flammable in air, but it is flammable at 11% in oxygen and 10% in

nitrous oxide.⁷ However, it is an unlikely candidate as a fuel because it is impossible to deliver those concentrations from a variable bypass vaporizer.

Hydrogen is poorly soluble in water and body fluids and could accumulate in low-flow anesthesia situations. Unlike many hydrocarbons, hydrogen has a wide flammability range, from 4% to 75% in air⁶ and from 4% to 94% in oxygen.⁸ In addition to carbon monoxide, sevoflurane is known to break down in contact with carbon dioxide absorbents to yield compound A, compound B, formaldehyde, methanol, and formate.⁹ Hexafluoroisopropanol is also a proposed breakdown product of sevoflurane. Formaldehyde has been shown to react in aqueous solution with strong bases such as NaOH to produce hydrogen gas and formate.¹⁰ The stability of methanol and formate in desiccating alkaline conditions has not been studied. These compounds may also contribute to hydrogen production. In addition, hexafluoroisopropanol is a proposed breakdown product of sevoflurane.⁹ The hypothesis that sevoflurane degrades in high-temperature-desiccated carbon dioxide absorbents to produce molecular hydrogen was tested. In addition, the formation of hydrogen from the sevoflurane breakdown products formaldehyde, formate, methanol, and hexafluoroisopropanol was examined to evaluate their possible role in sevoflurane-dependent hydrogen formation.

Materials and Methods

A reactor was constructed from a fused quartz tube of 2 mm wall thickness, 1.2 cm internal diameter, and 40 cm length. A fiberglass plug 8 cm from the bottom held 20 g of desiccated absorbent in place in the central 24 cm of the reactor. The internal volume of the reactor was 45 ml, and the volume of the tubing was less than 10 ml. The reactor was heated by wrapping the central 24 cm with nickel chromium resistance wire and providing current with a variable autotransformer (0-140 VAC, STACO variable autotransformer model 2PF1010; Dayton, OH). Reactor temperatures greater than 400°C could be produced with this setup. Barium hydroxide lime (Baralyme; Allied Health Care, St. Louis, MO) and soda lime (Sodasorb; W. R. Grace, Cambridge, MA) were desiccated by the flow of dry oxygen for 2 weeks (constant weight was attained during this time period) and then ground and sifted so that particles between 12 and 40 mesh were retained and used. The smaller particle size was used to increase surface area and to increase the

* Professor of Medicine and Physiology, † Research Scientist, Department of Biophysics, ‡ Research Fellow, Department of Anesthesiology, § Former Research Support, Department of Anesthesiology, || Professor of Anesthesiology, Medical College of Wisconsin.

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Address correspondence to Dr. Woehlck: Department of Anesthesiology West, Froedtert Memorial Hospital, 9200 West Wisconsin Avenue, Milwaukee, Wisconsin 53226. hwoehlck@mcw.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

amount of absorbent that the reactor would contain. Particles finer than 40 mesh were removed to reduce the pressure drop through the reactor. We used a 1-l foil-lined reservoir bag as the gas supply, which we filled with nitrogen gas under atmospheric pressure and room temperature. Reaction products were collected in a 1-l foil-lined gas sampling bag at atmospheric pressure and room temperature (QuinTron Instrument Co., Milwaukee, WI).

Experiments were performed at least in triplicate. For each experiment, the reactor was filled with 20 g of desiccated barium hydroxide lime or soda lime, which contained approximately 0.02 moles of univalent base. This was intended to represent a large excess of sodium or potassium hydroxide per mole of reactant. Nitrogen was flushed through the reactor at 0.5 l/min for 10 min from a regulated compressed cylinder source (BOC Gases, Milwaukee, WI) to remove oxygen that could potentially create a flammable mixture. The pressurized gas source was removed, and the gas reservoir and collection bags were connected. External heat was applied until the reactor reached the desired temperature. The temperature of the reactor was measured with an American National Standards Institute type J (Iron-Constantan) thermocouple (Simpson Electric Company, Elgin, IL). An analog temperature display was provided *via* a Simpson 388-3L thermometer (Simpson Electric Company). Control gas samples were taken before introducing the test substance into the heated reactor.

The disposition of the multiple fluorine atoms of sevoflurane or hexafluoroisopropanol remains unknown, but these could be converted to inorganic fluoride and potentially combine with many of the univalent base moieties. Therefore, we intended to use approximately 0.001 moles of volatile fluorinated reactant per experiment, resulting in approximately 20 moles of sodium or potassium hydroxide per mole of sevoflurane or hexafluoroisopropanol. We used approximately 0.003 moles of formaldehyde, methanol, or formate per experiment because these compounds are unhalogenated, resulting in 6–7 moles of univalent base per mole of reactant. After maintaining the temperature in the desired range for 10 min, 1.0 ml formalin, 10% (Fischer Scientific, Middleton, VA); 0.1 ml sevoflurane (Ultane; Abbott Laboratories, Abbott Park, IL); 0.1 ml methanol (Aldrich Chemical Co., Milwaukee, WI); or 0.1 ml hexafluoroisopropanol (1,1,1,3,3,3 hexafluoro-2-propanol; Aldrich) was injected into the tubing upstream of the reactor where it would be vaporized by the heat, followed by 1,000 ml nitrogen gas to flush the reactants and products through the heated absorbent within the first 5 min. One series of experiments tested the effect of water on hydrogen production from sevoflurane. In these experiments, 1.0 ml water and 0.1 ml sevoflurane were injected together. After 5 min, the collection bag was removed.

The reaction of sodium formate was conducted differ-

ently because it is solid at room temperature. A solution was made by dissolving 3.1 g sodium formate in the minimum quantity of room temperature water that allowed rapid dissolution of the solid (7.5 ml total volume). To produce an even distribution of formate throughout the absorbent, 0.2 ml of solution was sprayed as evenly as possible onto the absorbent before placing it into the reactor. The reactor was flushed with nitrogen at room temperature for 10 min before heating. The collection bag was then placed onto the downstream end of the reactor, and the reactor was heated. After 400°C was attained, 1,000 ml nitrogen was passed through the reactor as in the other experiments. The volume of gas in the collection bag was measured.

The gas was analyzed for hydrogen *via* gas chromatography using a packed column containing a 13X molecular sieve and measured with a thermal conductivity detector (model Q gas chromatograph; QuinTron Instrument Co., Milwaukee, WI). Using compressed hydrogen gas for calibration may pose a fire risk because hydrogen may ignite when released from a compressed gas cylinder due to static charges or heating upon expansion. To reduce the fire risk, we prepared a few milliliters of hydrogen at a time by dissolving aluminum metal in potassium hydroxide solution (Aldrich Chemical Co.). We desiccated the resulting hydrogen gas by passing it through anhydrous calcium sulfate (W.A. Hammond Drierite Co., Ltd., Xenia, OH) and prepared a 1% volumetric standard for gas chromatography calibration by diluting the hydrogen gas with nitrogen and placing it into a 1.5-l foil-lined gas collection bag (QuinTron Instrument Co.). During gas chromatography, hydrogen was measured using nitrogen as a carrier gas. The lower limit of detection was 125 ppm. The identity of hydrogen was confirmed by the identical residence time to the hydrogen standard and the same deflection (indicating greater thermal conductivity than nitrogen) as the standard. To confirm that sevoflurane was not present to interfere with the gas chromatography measurements, we measured the product gas with an Ohmeda RGM 5250 (Datex Ohmeda, Madison, WI) monitor and also a Marquette SAM monitor (Smart Anesthesia Multigas Module; GE/Marquette, Milwaukee, WI) to confirm that minimal concentrations of sevoflurane passed through the reactor unchanged. The quantity of hydrogen produced was determined by multiplying the concentration by the volume of gas produced for each experiment. The yield was determined by dividing the moles of hydrogen produced by the moles of reactant. The moles of reactant were calculated *via* molecular weight, density, and volume injected, and the moles of hydrogen produced were calculated *via* the measured volume, concentration determined by gas chromatography, and the ideal gas law. The results are displayed as mean \pm SD. In the experiments where methanol or formate were reacted, the absorbent was tested for the quantity of carbonate or

Table 1. Production of Hydrogen in Moles of Hydrogen per Mole of Reactant

Reactant	Temperature, °C	Barium Hydroxide Lime	Soda Lime
Control (n = 12)	300	ND	ND
Sevoflurane (n = 4)	55	0.12 ± 0.06§	ND*
Sevoflurane (n = 6)	100	0.44 ± 0.09§	0.08 ± 0.01†§
Sevoflurane (n = 6)	200	1.24 ± 0.03§	0.95 ± 0.03†§
Sevoflurane (n = 6)	300	2.97 ± 0.08§	2.87 ± 0.35§
Sevoflurane (n = 6)	400	2.80 ± 0.15§	2.76 ± 0.17§
Sevoflurane + water (n = 3)	300	2.22 ± 0.02†§	NP
Formalin (n = 3)	400	1.97 ± 0.05§	NP
Sodium formate (n = 3)	400	1.05 ± 0.01§	NP
Methanol (n = 6)	300	1.10 ± 0.45§	NP
Methanol (n = 5)	400	2.30 ± 0.09§	NP
Hexafluoroisopropanol (n = 5)	300	0.91 ± 0.07§	NP
Hexafluoroisopropanol (n = 3)	400	0.75 ± 0.03§	NP

Production is in terms of moles of hydrogen produced per mole of reactant introduced. ND indicates that no hydrogen was detected; values at the minimum detectable limit (125 ppm) were used for *t* test comparisons. For comparison, the hydrogen concentration shown using sevoflurane and barium hydroxide lime at 55°C was approximately 2,000 ppm. NP indicates this experiment was not performed.

* Soda lime values are different from barium hydroxide lime values, $P < 0.05$. † Soda lime values are different from barium hydroxide lime values, $P < 0.001$.

‡ Values are different from sevoflurane without water and barium hydroxide lime at 300°C, $P < 0.001$. § Values are different from control, $P < 0.001$.

bicarbonate produced during reaction by acidifying with 10% hydrochloric acid (diluted 37% hydrochloric acid solution; Aldrich) and collecting the gas over water. The net production was calculated by measuring the increase in carbon dioxide content after reaction compared with the content of an equivalent quantity of barium hydroxide lime before reaction with formate.

We performed two pilot experiments using an anesthesia machine and desiccated soda lime ($n = 2$). With the following exceptions, the experiments were performed with the same equipment as Holak *et al.*¹ To prevent ignition, nitrogen was used instead of oxygen to run the ventilator and as the fresh gas. Type J thermocouples were inserted into the center of each absorbent canister to measure temperature, and gas samples were measured for hydrogen. The conditions were otherwise exactly the same as the previously published experiment where explosion and fire resulted.¹ We did not have sufficient unexpired barium hydroxide lime to perform experiments in an anesthesia machine.

Statistics

Unpaired two-tailed *t* tests were calculated *via* spreadsheet (Excel; Microsoft Corporation, Cupertino, CA). The Bonferroni correction was applied for multiple comparisons where applicable.

Results

In the temperature-controlled reactor, up to 3 moles of hydrogen were produced per mole of sevoflurane at 300°C and 400°C in both soda lime and barium hydroxide lime (table 1). Lesser amounts of hydrogen were produced at lower temperatures. Differences between soda lime and barium hydroxide lime were only apparent at temperatures below 300°C, where soda lime pro-

duced less hydrogen than barium hydroxide lime. Each mole of formaldehyde produced approximately 2 moles of hydrogen at 400°C. Formate and hexafluoroisopropanol both produced approximately 1 mole of hydrogen per mole of reactant at high temperatures. A slight decrease in hydrogen production was observed when 1.0 ml water was injected with 0.1 ml sevoflurane. Methanol produced approximately 2.3 moles of hydrogen per mole reacted. We found that 0.97 ± 0.01 moles of carbon dioxide were produced for each mole of methanol reacted, and 0.92 ± 0.02 moles of carbon dioxide were produced for each mole of formate reacted. Pilot experiments in the anesthesia machine are described in the Discussion.

Discussion

Our data demonstrate that up to 3 moles of hydrogen can be produced by the breakdown of sevoflurane in an excess of desiccated absorbent at high temperatures. Smaller amounts of hydrogen were produced at lower temperatures. It seems that 300°C is the minimum temperature that makes this process occur rapidly. The mechanisms by which sevoflurane produces hydrogen cannot be conclusively confirmed in this study. However, the data suggest that hydrogen could be formed *via* the known breakdown pathways of sevoflurane on base. Sevoflurane initially breaks down to produce formaldehyde, inorganic fluoride, and hexafluoroisopropanol (fig. 1A).⁹ Isolation of free hexafluoroisopropanol has not been reported, presumably because it is a highly acidic alcohol and would exist as an absorbent-bound hexafluoroisopropoxide ion in alkaline materials such as soda lime. Formaldehyde is also expected to be bound to the absorbent after conversion to the geminal diol by hydroxide, and the equilibrium in favor of ionization of

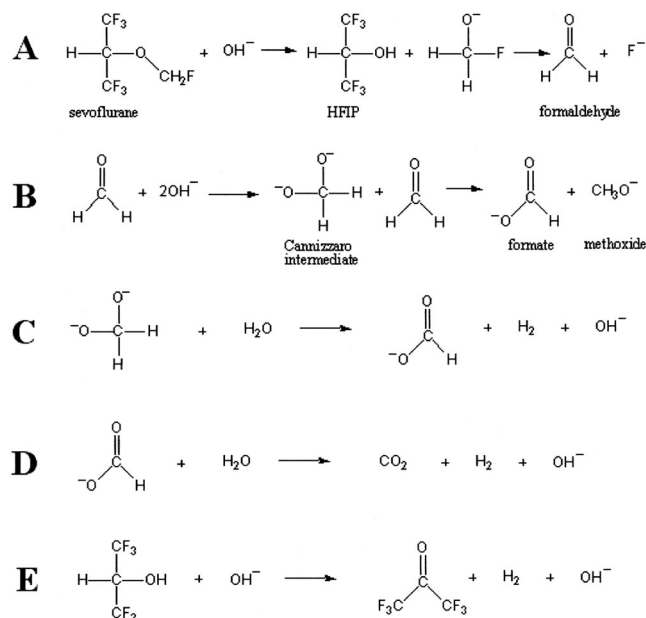


Fig. 1. Schema of the proposed breakdown pathways of sevoflurane that produce hydrogen. (A) A proposed initial breakdown pathway in which sevoflurane reacts with hydroxide to produce inorganic fluoride, formaldehyde, and hexafluoroisopropanol (HFIP) as suggested by Glassman.⁶ (B) The formation of the Cannizzaro intermediate, which is the doubly ionized geminal diol of formaldehyde, and the classic Cannizzaro reaction, which produces methanol (as methoxide ion) and formate. (C) The formation of hydrogen and formate by reaction of the Cannizzaro intermediate with water. (D) The breakdown of formate to produce hydrogen gas and carbon dioxide, which would most likely exist as absorbent bound carbonate. (E) The reaction of HFIP, an acidic alcohol, that will ionize in the presence of the more basic hydroxide ion to produce the hexafluoroisopropoxide ion. Hexafluoroisopropoxide has only one hydrogen atom that can be donated as hydride to produce dihydrogen gas. We did not attempt to isolate the proposed end product, hexafluoroacetone, which is a toxic, highly reactive electrophile¹⁴ and would likely exist as an absorbent bound hydrate.¹⁵

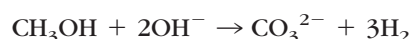
the geminal diol would also keep formaldehyde bound to the absorbent as an ionic compound.¹⁰ Consistent with this hypothesis, at temperatures that reached just over 100°C, Funk *et al.*¹¹ found low gas phase concentrations of formaldehyde during simulated induction with dry potassium hydroxide-containing limes, but the methanol concentration was 500 times greater, demonstrating that considerable quantities of formaldehyde were formed and underwent further reaction *via* the Cannizzaro mechanism while bound to the absorbent.

The Cannizzaro intermediate (the doubly ionized form of the geminal diol of formaldehyde) donates a hydride ion to another molecule of formaldehyde to produce formate and methoxide in the classic Cannizzaro reaction (fig. 1B). This reaction can only occur if the free formaldehyde concentration allows interactions between two formaldehyde molecules. The methoxide ion would subsequently react with any available proton to produce free methanol. Previous literature shows that when formaldehyde is present in low concentrations, it

may be converted directly to formate in solution by reaction of the Cannizzaro intermediate with water, producing hydrogen gas (fig. 1C).¹⁰ Formaldehyde-formaldehyde reactions are unlikely to occur at low concentrations in aqueous solution, and this situation may also exist in desiccated absorbent where formaldehyde is chemically bound to the absorbent. Because desiccated absorbent should have little free water, it remains possible that other hydride acceptors exist that may result in dihydrogen production. One possibility is that sufficient water of hydration may remain after desiccation to constant weight to allow hydrogen production to occur. Alternatively, hydride transfer may occur to the hydroxide moiety of less basic absorbent components, such as calcium hydroxide, generating dihydrogen, calcium oxide, and hydroxide ion. This latter possibility may allow for dihydrogen production in the absence of free water. Our experiments have not distinguished between these proposed reaction pathways.

Because 2 moles of hydrogen were produced by formaldehyde, our data support the hypothesis that formate, which is formed from formaldehyde, can undergo further reaction to produce 1 of these 2 moles of hydrogen. The concurrent formation of carbon dioxide supports the reaction of formate (fig. 1D) with water on base to form hydrogen.

Methanol is produced from formaldehyde *via* the Cannizzaro reaction (fig. 1B). Our results demonstrate that methanol is not stable in desiccated barium hydroxide lime at 300°–400°C and will break down to form hydrogen and absorbent-bound carbon dioxide, most likely as carbonate.



The significance of this finding is that even if methanol were formed *via* the Cannizzaro reaction, methanol can contribute to the production of hydrogen gas if the absorbent temperature becomes sufficiently high.

Sevoflurane produces up to 3 moles of hydrogen, and 2 of these may be formed by the breakdown of formaldehyde and formate, which includes the possible formation and subsequent destruction of methanol. The data support the hypothesis that hexafluoroisopropanol can contribute to hydrogen formation. Hexafluoroisopropanol produces up to 1 mole of hydrogen in desiccated absorbent at 300°–400°C. A proposed breakdown reaction is shown in figure 1E.

Adding 1.0 ml water to 0.1 ml sevoflurane decreased the production of hydrogen from sevoflurane breakdown by only 33% at 300°C. Similarly, 10% formalin seemed to react completely even though most of the mass of the reactants was water. Once heated to 300° or 400°C, it seems that there is little effect of water on the production of hydrogen as a breakdown product of sevoflurane or formaldehyde. Conversely, during normal

clinical use at or near room temperature, anesthetics are generally stable in hydrated absorbents.

We performed pilot experiments in an anesthesia machine in an attempt to measure hydrogen concentrations when desiccated absorbent self-heats to extreme temperatures.¹ Temperatures greater than 400°C may result when desiccated, unexpired barium hydroxide lime reacts with sevoflurane.¹² In our study, soda lime produced in a peak temperature of 106°C and a peak hydrogen concentration of less than 0.5%. These temperature values with soda lime are consistent with the results of another recent study.¹³ Although soda lime produced large amounts of hydrogen when externally heated in this study, desiccated soda lime did not self-heat to the temperatures required for large amounts of hydrogen production in an anesthesia machine.

Although produced in a small, temperature-controlled reactor, the results are clinically relevant because previous studies have shown that sevoflurane and desiccated barium hydroxide lime can self-heat to temperatures greater than 400°C.¹² The results support the hypothesis that flammable quantities of hydrogen gas may be produced if sevoflurane reacts with desiccated barium hydroxide lime. It has been reported that high sevoflurane vaporizer settings were used when anesthesia machine fires have occurred. If 3 moles of hydrogen are produced from each mole of sevoflurane, then the hydrogen concentration can theoretically be 3 times the sevoflurane vaporizer setting under steady state conditions. It is possible that up to 24% hydrogen can be produced if the absorbent temperature exceeds 300°C and the vaporizer is set at 8% sevoflurane. This is well above the lower flammable limit of hydrogen of 4%. Other flammable breakdown products may have been present but were not measured in this study. The presence of flammable hydrocarbons would not be required for the formation of a flammable gas mixture with these concentrations of hydrogen.

Hydrogen is very insoluble in water and body tissues and is unlikely to be removed from the breathing circuit by the lung. This property promotes the formation of a flammable gas mixture when hydrogen is produced. Temperatures of greater than 400°C have been docu-

mented during sevoflurane breakdown, but these were well below the autoignition temperature of hydrogen (560°C).⁶ Flammable hydrogen gas mixtures are easily ignited, in part because the ignition energy of hydrogen is an order of magnitude lower than that of hydrocarbons.⁶ Static electricity or trace amounts of catalytic metals or oxides are likely causes of ignition (personal verbal communication with Andrew McIlroy, Ph.D., Manager, Combustion Chemistry, Sandia National Laboratories, Livermore, California, July 2005).

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