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Effect of temperature and some common metals on the stability of volatile anaesthetic–Entonox mixtures

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Abstract

Thermal stability of pressurised ready-to-use volatile liquid anaesthetic mixtures (halothane, isoflurane and enflurane) in Entonox (commercially available premixed 50% N_2O, 50% O_2 mixture) were investigated at temperatures of 20, 258, 400, 503 and 602°C on glass, stainless steel, copper and aluminium by gas chromatography and GC–MS. It was found that most of the decomposition products formed were halogenated compounds and the observed thermal stabilities in glass, stainless steel and copper allowed a thermal treatment up to 250°C without any decomposition problem. Aluminium was found to be the most effective metal at causing decomposition of the anaesthetic mixtures even at lower temperatures.

Keywords: Entonox; Halothane; Isoflurane; Enflurane

1. Introduction

In a recent publication, high-pressure behaviours of liquid anaesthetics [halothane (2-bromo-2-chloro-1,1,1-trifluoroethane); isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) and enflurane (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether)] in Entonox (commercially available 50% N_2O, 50% O_2 mixture) were investigated up to 10.0 MPa pressures and nonideal behaviours have been utilised to prepare the premixed cylinder mixtures [1]. The cooling effect due to rapid expansion of gas during discharge causes a layer of ice to form on the metal parts of the valves where actual expansion of the compressed gas occurs and cooling may change the vapour concentration of the liquid anaesthetics in the discharged one phase gas mixtures. A possible alternative to this effect could be a thermal stabilisation of the valve body by means of an electrical device [2]. Although the temperature needed for the thermal stabilisation would not be high, every case should be taken into consideration before making any suggestions in a delicate field of practice.

No information is available on the thermal stability of volatile anaesthetics, and the possible effects of metals on this stability and on the decomposition products. Since such mixtures contain oxygen in high proportions, heating in contact with a metal may cause decomposition which produces a series of unknown substances even at lower temperatures by the catalytic effect of metals/metal oxides.

A little information is obtained from the manufacturer's instruction sheets on the corrosive effects of anaesthetics. The only available test on halothane [3]

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demonstrated that after exposure to moist halothane vapour in the presence of oxygen for 14 days, various metals reacted as follows at room temperature: nickel, titanium, no action; brass, silver, copper, phosphor-bronze, stainless steel, slight tarnishing; lead, aluminium–nickel alloy, some corrosion; magnesium, aluminium, tin, zinc alloy, definite corrosion. Laboratory tests performed at room temperature do not give a satisfactory answer to the question under investigation and experiments were designed to investigate the effect of temperature and metals on the stability of premixed halothane (isoflurane or enflurane) in Entonox. The investigated temperature limits were extended from room temperature to 600°C to obtain useful data for further studies. Common metals which are commercially available as tubing, such as copper, aluminium, stainless steel were chosen as test metals and glass was used as an inert reference material.

2. Experimental

2.1. Test mixtures and materials

The static mixtures of halothane (May and Baker, Dagenham, UK), isoflurane or enflurane (Rhône-Poulenc, Bristol, UK), at about 1% v/v, were prepared gravimetrically in Entonox in 4.67-l water capacity cylinders, at about 5.0 MPa pressures. Entonox was purchased from B.O.C. and used without further purification. A tube oven (Griffin and George, Loughborough, UK) equipped with a 7.6 A temperature controller (Eurotherm) was employed to change the temperature from 20°C to 600°C. Oven temperatures were calibrated prior to experiment. Working temperatures were 20, 258, 400, 503 and 602°C. Lengths (2 m) of tubing of glass (5 mm) and aluminium, copper and stainless steel (3 mm) were wound into 15-mm diameter coils to make the test pieces, giving an internal volume of about 40 and 15 cm^3, and internal surface area of 315 and 190 cm^2, for glass and metal tubes, respectively. Glass was employed to test the temperature effect alone on the stability of the mixtures. The flow-rates of the mixtures were set at not more than 10 ml/min to give the substances a contact time of >1 min with the metal surfaces. A soap bubble flow meter was used to measure the flow-rates at the outlet of the gas switching valve for at least 4 min before the first sample was taken for analysis.

2.2. Gas chromatography

Gas chromatography was chosen as a tool to monitor the substances. A Perkin Elmer F-33 gas chromatograph equipped with an flame ionisation detector (FID) and six port gas switching valve (Perkin Elmer) with a 0.75-ml sample loop was employed. N_2 was used as carrier gas at 7.5 p.s.i.g. inlet pressure. A 2-m silicone oil OV 101, (80–100 mesh particle size) 1/4-inch O.D. stainless steel column was used and the oven temperature was 100°C. Detector responses were converted into chromatograms by a Hewlett-Packard HP3396A computing integrator. Halothane, isoflurane and enflurane contain halogen atoms and halogenated acids such as HCl, HBr, HF are likely to be produced in the decomposition process. FID fails to detect such components. To detect such acids and overlapping peaks of the other acidic components, wet chemistry was employed in conjunction with GC and the effluent gases were bubbled into a solution of Bromo Cresol purple indicator ($pK_a=6.12$) in 100 ml distilled water.

2.3. GC–MS analysis

GC–MS analysis was performed using a Hewlett-Packard 5970 mass selective detector with sample introduction into the mass spectrometer via an HRGC 5160 Mega series gas chromatograph equipped with a 50 m×0.33 mm I.D. capillary column with a 0.5-μm thickness of silicone oil (BP1). Carrier gas (purified helium) inlet pressure was 0.325 bar (4.82 p.s.i.g.). The column temperature was programmed from 50°C to 120°C at a rate of 10°C/min. A 0.1-μl sample was injected directly into the column with a long needled 0.5-μl syringe. Evaluation of the chromatograms was performed by a computer programme. Each substance peak yielded a complete mass spectrum. These spectra were then compared with those in the computer's library according to the similarity index.

2.4. Sampling procedure

The tubing was connected to the experimental system and the desired oven temperature was adjusted. Helium was continuously flushed through the tubing to prevent preoxidation of the metal tubes until the desired temperature was reached. Then, helium flow was stopped and a mixture cylinder was connected to the system. The cylinder contents were released continuously at a flow-rate of 10 ml/min. Connection between the oven outlet and the GC was made through a piece of stainless steel 1/16-inch tube (40 cm) which was heated to 100°C by sending a hot air flow to prevent condensation.

(1) For gas chromatographic analyses, at least two samples were taken for each mixture directly by switching the valve on position to see the repeatability of the chromatograms. This procedure was repeated for each tubing and temperature with each mixture.

(2) To collect effluents for GC–MS analyses, the 5-ml glass bottles were immersed into liquid nitrogen and effluents were directed into the bottles by switching the valve on position. Following sample collection for 3 min bottles were removed from the cooling environment and diluted with isooctane immediately by pouring it on to the solid-phase (if isooctane is put into the bottle first it freezes and volatile components are lost) and solutions in the stoppered bottles were warmed up to room temperature. This procedure was repeated for each tubing with each anaesthetic mixture at 600°C for glass, 500°C for stainless steel and copper, and 400°C for aluminium. The layout of the system used is shown in Fig. 1.

3. Results and discussions

The conditions employed for GC were not ideal for excellent separations. As no information was available for the decomposition products and their retention times, the inlet pressure of the nitrogen gas (10 p.s.i.g.) and the oven temperature (100°C) were selected to obtain reasonable separations. The retention times of the last substances should not be less than 10 min to provide the adequate retardation in the column. The low flow-rate for the carrier gas means poor separation. However, this does not necessarily mean that the single peaks on the chromatograms overlaps with some decomposition products. The colour of the indicator solution forewarns the analyst if any decomposition has taken place with a single peak appearing on the chromatogram. The

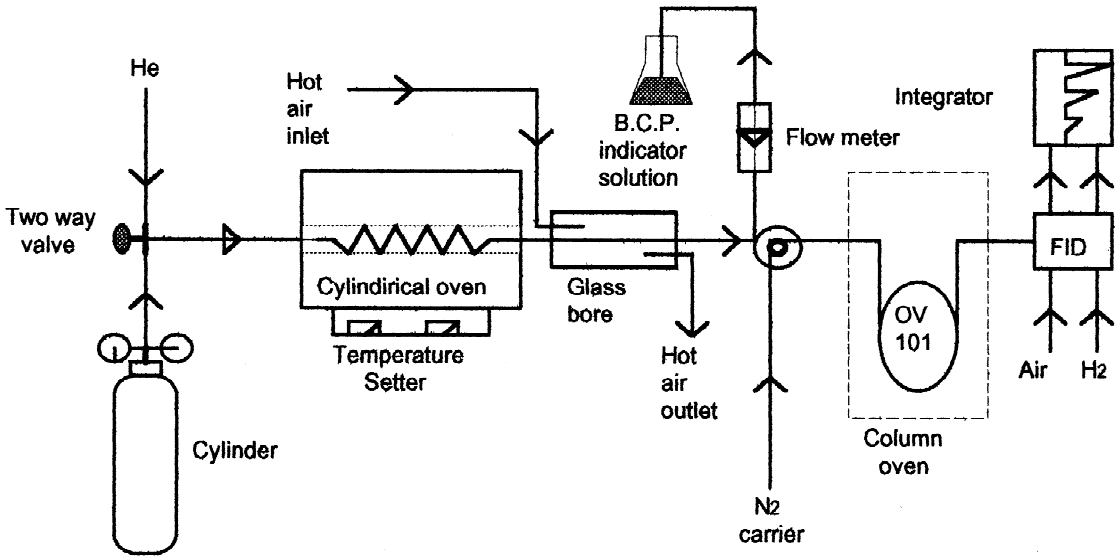

Fig. 1. Experimental layout of the system used in the thermal stability experiments.

chromatogram of isoflurane given in Fig. 5 at 400°C on aluminium represents such a situation. Bromo Cresol purple was used because of its very narrow transition pH (5.2–6.8) and its convenient colour change from purple to yellow. For instance, ~$6.3 \cdot 10^{-7}$ mol of H^+, are needed to lower the pH of 100-ml of indicator solution from 7.0 to 5.2. Even 0.10% acid conversion which come from the decomposition of total volume of 15 cm^3 anaesthetic mixtures (about total of $6.2 \cdot 10^{-4}$ mol) would be enough to observe the full transition from purple to yellow colour.

GC data given in Fig. 2 show that the volatile anaesthetic–Entonox mixtures were very stable on glass (used as inert material) in comparison to metals. THe observed decomposition temperature of 602°C for halothane and isoflurane and 503°C for enflurane may not be surprising when one considers the synthesis temperatures of the volatile anaesthetics and the stabilities of the molecules [4]. The formed compounds obtained from GC–MS evaluation are numbered in Table 1 as 1–5; 17, 18; 25, 26, respectively. Decomposition starts at lower temperatures when metals are used instead of glass. Stainless steel is known to be relatively inert and stable in comparison with aluminium and copper. However, Fig. 3 shows that this metal causes a fall in the decomposition temperature, and decomposition for halothane, isoflurane and enflurane started at 503°C, 400°C and 400°C and produced 6–10; 19, 20; 27, 28 numbered compounds respectively (Table 1). With copper, decomposition started at 500°C for halothane, isoflurane and enflurane. Fig. 4 shows that changing to copper elevates the decomposition temperature for enflurane and isoflurane by about 100°C and changes the chromatographic pattern for halothane. With this metal, halothane, isoflurane and enflurane produced 11–13; 21,22; 29–31 numbered compounds (Table 1) respectively. Aluminium caused most decomposition of the volatile anaesthetic mixtures. Isoflurane and enflurane were easily decomposed on aluminium (see Fig. 5) even at a temperature of 258°C. The effect of this metal was not, however, the same for halothane which has no ether linkage, and its decomposition started at 400°C. The compounds produced are given in Table 1 as 14–16; 23, 24; 32–35. Among the investigated anaesthetics, halothane decomposed to produce most different substances under all experimental conditions. In the GC–MS analysis no peak was observed for nitrous oxide and halogenated acids. This may show that despite all the precautions taken the light gases (inorganic) and decomposition products (organic and inorganic) with low molecular masses could not be trapped efficiently in isooctane.

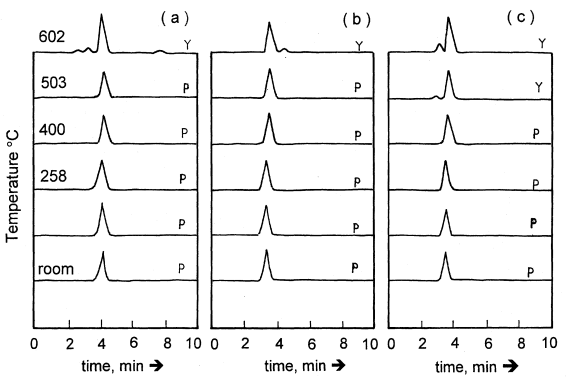

Fig. 2. Chromatographic thermal stability pattern of (a) halothane, (b) isoflurane and (c) enflurane in Entonox in glass. Colour of the indicator solution P: purple, Y: yellow.

According to the decomposition chromatograms the stability of the volatile anaesthetic mixtures depends on the metal used rather than on the temperature alone. The changes in the decomposition temperature and the chromatographic pattern may indicate some additional catalytic effect of metals on the stability of the volatile anaesthetics. The number of peaks and their observed retention times in the chromatograms showed that even at the same decomposition temperature for a substance with different metals, different compounds may be produced. Because the mixtures contain a high percentage of oxygen and decomposition produces acidic gases it may be difficult to talk about a purely metallic effect, a metal/metal oxide combined effect should be considered at higher temperatures. The oxide layers in the inner surface of the tube due to oxidation of the metals caused adsorption problems for the volatile anaesthetics and their decomposition products. These adsorbed compounds were later released and resulted in ghost peaks causing confusion. For example, halothane or isoflurane appeared as small peaks at the right retention times during enflurane experiments or vice versa. These may be prevented by taking some precautions.

Table 1
Library identities of the decomposition products of anaesthetics in glass, stainless steel, copper and aluminium tubing at elevated temperatures

No.	t_R	M_r	SI	Product library name	Peak size
Halothane					
in glass, 600°C					
1	2.30	198	92	2-Chloro-1,1,1,4,4,4-hexafluoro-2-butene	Medium
2	2.70	232	88	2,3-Dichloro-1,1,1,4,4,4,-hexafluoro-2-butene	Medium
3	2.82	196	85	Halothane	Major
4	4.60	150	85	1-Bromo-2,2-dimethylpropane	Medium
5	9.20	112	77	2-Bromo-2-methylpropane	Big
in stainless steel, 500°C					
6	2.28	170	86	1,1-Dichloro-1,2,2,2-tetrafluoroethane	Big
7	2.50	152	92	2,2-Dichloro-1,1,1-trifluoroethane	Medium
8	2.82	196	88	Halothane	Major
9	4.68	150	91	1-Bromo-2,2-dimethylpropane	Small
10	9.20	112	71	2-Bromo-2-methylpropane	Big
in copper, 500°C					
11	2.23	136	69	1-Chloro-1,1,2,2-tetrafluoroethane	Small
12	2.82	196	85	Halothane	Major
13	4.55	150	77	1-Bromo-2,2-dimethylpropane	Medium
in aluminium, 400°C					
14	2.70	176	77	1-Bromo-1-chloro-2,2-difluoroethene	Small
15	2.82	196	88	Halothane	Major
16	3.30	432	45	Heptachlorohexafluorohexane	Small
Isoflurane					
in glass, 600°C					
17	2.37	182	54	2-Chloro-1(chloromethoxy)-1,1,2-trifluoroethane	Medium
18	4.30	160	57	1-Fluorodecane	Small
in stainless steel, 500°C					
19	2.23	136	68	1-Chloro-1,1,2,2-tetrafluoroethane	Medium
20	2.48	152	88	2,2-Dichloro-1,1,1-trifluoroethane	Medium
in copper, 500°C					
21	2.23	102	54	1,1,2,2-Tetrafluoroethane	Medium
22	2.47	182	54	2-Chloro-1(chlorometoxy)-1,1,2-trifluoroethane	Major
in aluminium, 400°C					
23	2.20	136	67	1-Chloro-1,1,2,2-tetrafluoroethane	Major
24	3.16	118	91	Chloroform	Medium
Enflurane					
in glass, 600°C					
25	2.42	184	86	Enflurane	Major
26	2.65	136	57	1-Chloro-1,1,2,2-tetrafluoroethane	Small
in stainless steel, 500°C					
27	2.42	184	86	Enflurane	Major
28	2.47	117	79	N,N-Dimethyl-2-ethoxyethylamine	Medium
in copper, 500°C					
29	2.23	102	54	1,1,2,2-Tetrafluoroethane	Medium
30	2.47	182	54	2-Chloro-1(chlorometoxy)-1,1,2-trifluoroethane	Major
31	3.16	118	91	Chloroform	Small
in aluminium, 400°C					
32	2.16	86	95	Chlorodifluoro, methane	Medium
33	2.38	102	93	Dichlorofluoro, methane	Medium
34	2.42	184	88	Enflurane	Major
35	3.16	118	91	Chloroform	Medium

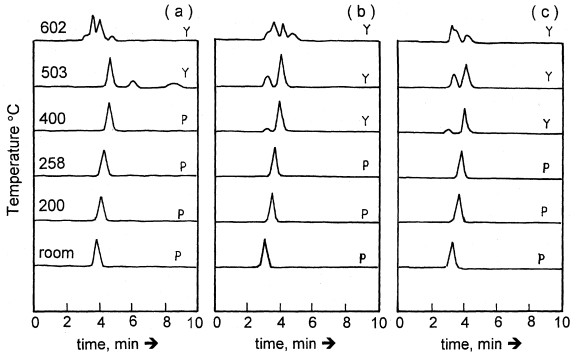

Fig. 3. Chromatographic thermal stability pattern of (a) halothane, (b) isoflurane and (c) enflurane in Entonox, in stainless steel. Colour of the indicator solution P: purple, Y: yellow.

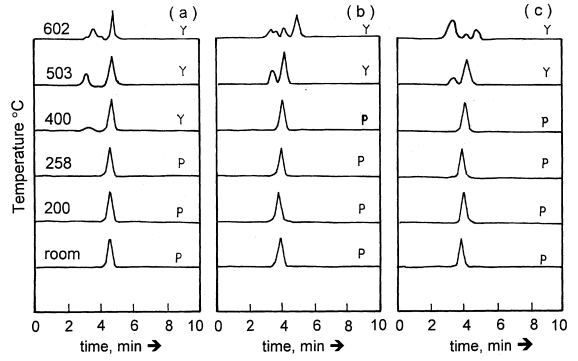

Fig. 4. Chromatographic thermal stability pattern of (a) halothane, (b) isoflurane and (c) enflurane in Entonox, in copper. Colour of the indicator solution P: purple, Y: yellow.

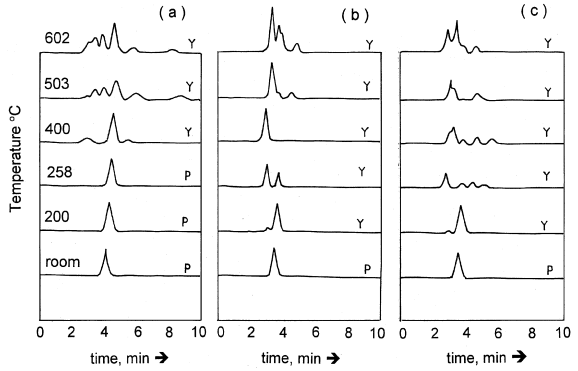

Fig. 5. Chromatographic thermal stability pattern of (a) halothane, (b) isoflurane and (c) enflurane in Entonox, in aluminium. Colour of the indicator solution P: purple, Y: yellow.

(1) Following the analysis of one mixture, helium should always be flushed through the tubes at a high flow-rate until the oven reaches the adjusted temperature. This prevents preoxidation of the metals before experiments.

(2) If any decomposition is observed, flushing helium even at a high flow-rate does not help to remove previous reaction products. In such circumstances the metal tube, gas switching valve and sample loop are washed with an organic solvent such as diethyl ether and dried with helium.

4. Conclusions

The experimental technique provides information about the temperatures at which decomposition of the anaesthetics approximately start and to some extent the effect of metals on these temperatures and the identities of the formed decomposition products. Usually, at the first stage of decomposition for each anaesthetics there are not that many peaks in the chromatograms. At higher temperatures an increase in the number of peaks may indicate further decomposition of the products rather than decomposition of the original starting materials. No decomposition was observed at 250°C with glass, stainless steel and copper tubing. The first peaks resulting from decomposition appeared at 400°C. Since no experiment were carried out at intermediate temperatures, it is difficult to ascertain the temperature at which the decomposition starts. However, 250°C may be considered a safe temperature limit for heating such mixtures in the absence of aluminium (as well as alloys containing aluminium) for any purpose. The experiments showed that some metals (e.g. aluminium) in conjunction with temperature are very effective at causing decomposition and before heating these mixtures in contact with such metals even at lower temperatures the effectiveness of the contact material must be investigated and the surface of the metal should be rust free to prevent metal/metal oxides catalytic effect. The colour of the indicator solution also indicates emergence of halogenated acids after the decomposition process and creates serious health and corrosion problems. In addition to this, most of the formed substances determined by GC–MS analyses are halogenated compounds and

those are likely to be harmful to human health whenever they are present in the mixtures. Although no quantitative evaluation has been performed, the peak sizes given in the last column of Table 1 show that the decomposition ratio is remarkable in the investigated conditions. The method used in this study has many limitations. A better approach would involve connecting the GC–MS in a series of the experimental system, employing a reaction column filled with metal chips instead of metal tubing, via a suitable packed column system for efficient and reliable separation of the light components. But this approach has serious drawbacks since the corrosion of the metal parts is one of the main problems.

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