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Evaluation of the mass spectrometric patterns of volatile liquid anaesthetics to predict the temperature—metal caused decomposition pathway

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Abstract

In this study, prediction of the thermal decomposition pathway of the volatile liquid anaesthetics such as halothane, enflurane and isoflurane in contact with various metal/metal oxides at elevated temperatures has been deduced by evaluating the mass spectrometric fragmentation pattern of each anaesthetic observed in the ionisation process. In the light of the molecular structures and fragmentation components, it was believed that the thermal decomposition pathway of each anaesthetic on metal/metal oxide surface, particularly at higher temperatures, is similar to the ionisation mechanism occurring in the mass spectrometer ionisation process with minor differences for each molecule. The ionisation clusters for each anaesthetic molecule show the most likely fragment and radicals formed in the mass spectrometric ionisation process by considering the isotopic effect. From these clusters, thermal decomposition pathway of the liquid anaesthetics and formation mechanisms of the major halogenated thermal decomposition products have been predicted. It was concluded that the ionisation and thermal decomposition pathway resembles each other, but are not completely similar.

Keywords: GC–MS; Thermal decomposition; Anaesthetics; Halothane; Enflurane; Isoflurane

1. Introduction

The most important agent in practical anaesthesia today is nitrous oxide, to which oxygen is necessarily added. Because nitrous oxide lacks potency, it is usually administered with additional more potent anaesthetic agents such as halothane (2-bromo-2-chloro-1,1,1-trifluoroethane), enflurane (2-chloro-1,1,2,-trifluoroethyl difluoro-methyl ether) or its isomer, isoflurane (1-chloro-2,2,2,-trifluoroethyl difluoromethyl ether) by adding the anaesthetic vapour to the inhaled gas stream by means of a vaporizer [1–3].

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In recent years, however, the pre-mixed and pressurized ready-to-use cylinder mixtures of a volatile anaesthetic (particularly isoflurane) prepared in Entonox (commercially available 50% N_2O, 50% O_2 mixture) is medically recommended by Tunstal and Ross [4] for analgesic purposes at lower concentrations (e.g. Isonox 0.25%). The extended high-pressure studies [5] showed that main problem with the pressurized cylinders in practice is that the cooling effect (cooling or freezing the cylinder body and valves). The rapid expansion of the pressurized gas phase to atmospheric pressure causes condensation of the liquid anaesthetics in cylinders and disturbs the stability of the stated gas phase concentration, which is very dangerous during medical practice. As a rapid solution, one may think that this problem could be solved easily by warming the cylinders or valves body by means of electrical heating devices on heavy demand. But, it should be born in mind that liquid anaesthetics contain halogen atoms and they are always used with oxygen in high proportion for anaesthetic purposes. Therefore, any thermal treatment of such mixtures in contact with metal/metal oxides, even at lower temperatures needs care and might result in halogenated toxic liquid or gas production [6].

In our previous study, the most commonly used volatile anaesthetics were decomposed in glass, stainless steel, copper and aluminium tubing in the 20–600 °C temperature range and the mass spectrometric analysis of trapped decomposition products has been performed. Aluminium was found as the most effective metal among the others and decomposition in aluminium started at lower temperatures (20–200 °C). No decomposition was observed up to 250 °C with glass, stainless steel and copper tubing. Therefore, 250 °C was considered a safe temperature limit for heating such mixtures in the absence of aluminium (or alloys containing aluminium) [6]. Although preventing the thermal decomposition of the anaesthetics during valve heating is the main purpose, if any, it would be invaluable to know the identities of the decomposition products. The identities of the formed decomposition products in furnace have been determined by mass spectrometer according to their similarity index (SI), representing the relation between the real compound and the computer library suggested compound. Nevertheless, none of the SI values for the identified compounds was found to be 100% in the experiments. Analysing the mass spectra of the anaesthetic molecules visually may assist in predicting more accurate identities or at least controlling the correctness of the identity of the furnace decomposition products by using the ionisation fragments up to some degree, but visual comparisons alone do not clear the identity problem completely. Besides visual analyses, it should also be proved if the studied anaesthetics would yield decomposition products similar to proposed identities by assuming ionisation and furnace mechanisms resemble each other. Therefore, the possible thermal decomposition pathway of the anaesthetic molecules and formation mechanism of new halogenated decomposition products have been predicted by the help of the designed ionisation clusters for more accurate identities and also to validate the assumption.

2. Experimental

Gravimetrically prepared 1% volatile liquid anaesthetic—Entonox (pre-mixed 50% N_2O and 50% O_2) mixtures (5.0 MPa) were decomposed in tubes (2 m × 3 mm i.d.) made of various materials such as glass (as reference material), stainless steel, copper and aluminium

(wound in a 15 mm diameter coils) by placing them in a tube oven (Griffin & George, UK) equipped with a 7.6 A temperature controller (Eurotherm) between 20 and 600 °C at <10 ml/min flow rate. To collect the effluents for GC–MS analyses 5 ml glass bottles were immersed into liquid nitrogen and effluents were directed into the bottles and after 3 min, solid phase deposited were diluted with isooctane immediately. 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 0.33 MPa (4.82 psig). The column temperature was programmed from 50 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 ml syringe. Using the computer programme of GC–MS evaluation of the resulted chromatograms was performed spontaneously. Each substance peak on the chromatogram yielded a complete mass spectrum. These spectra were then compared with those in the computer's library according to the SI.

3. Results and discussion

A number of halogenated products after decomposition have been observed for halothane, enflurane and isoflurane in various metal tubing at 20–600 °C temperature interval. Decomposition products whose peak size is small were neglected at the first step of study for the sake of simplicity. Therefore, only the major peaks, which were produced in significant quantities in the process, were taken into consideration in the pathway evaluation for each anaesthetic. The major halogenated thermal decomposition products determined by the GC–MS analysis are presented in Table 1 with the relevant metal and temperature values. In addition to halogenated organic compounds, some highly toxic and corrosive gaseous inorganic halogenated products such as HBr, HCl, HF (detected by Bromo Cresol purple indicator) and Br_2, which could not be trapped into the solution, have also been observed at low concentration level at the end of the all types of metal tubing [6].

The identity of the observed halogenated decomposition products is decided according to SI given by the computer library. One of the best ways for the checking of the correctness of the suggested identities is to compare the mass spectral fragments of the observed decomposition products and the library suggested compounds fragmentation patterns. Following this comparison, almost all of the compared mass spectra of the products are found very similar to the suggested formulas with minor differences. Nevertheless, none of the SI values are found 100% indicating that there is some doubt on the proposed identities.

More complex and tedious way of checking the suggested identities is through investigation of the mass spectrum of each pure anaesthetic molecule according to its fragmentation pattern and evaluation of the possibility of the formation of the suggested formulas by combining these fragments. However, this approach assumes that the furnace and mass spectrometric ionisation process is very similar. On the other hand, this assumption helps us to predict the thermal and metal caused decomposition mechanism for each anaesthetic otherwise impossible, as no other information is available. As a starting point, the mass spectrum of each anaesthetic molecule inspected according to its fragmentation pattern, which is unique for each compound. The fragments arise from the rupture of the molecular

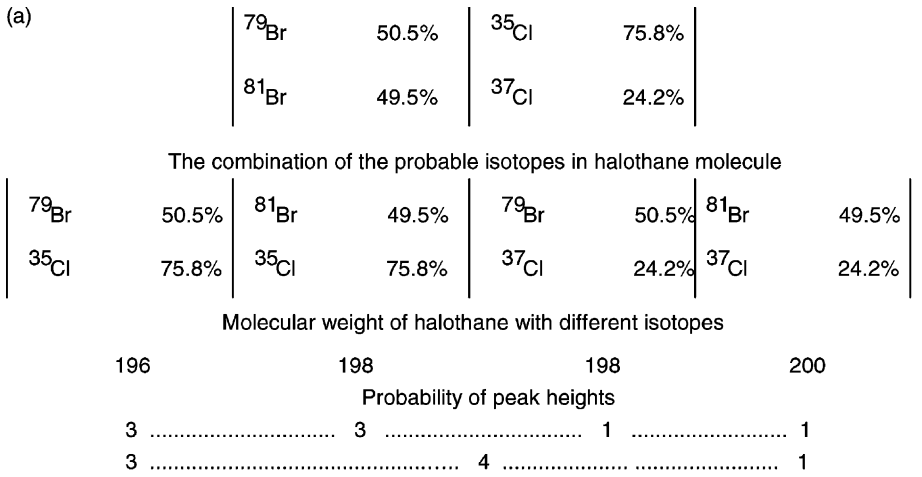
Table 1
Major furnace formed products for halothane, enflurane and isoflurane in various metal tubing at 20–600 °C interval

No.	M_r	SI	Product name
Halothane			
1	112	77	2-Bromo-2-methylpropane[a]
2	150	85	1-Bromo-2,2-dimethylpropane[a]
3	152	92	2,2-Dichloro-1,1,1-trifluoroethane[b]
4	170	86	1,1-Dichloro-1,2,2,2-tetrefluoroethane[b]
5	198	92	2-Chloro-1,1,1,4,4,4-hexafluoro-2-butene[a]
6	232	88	2,3-Dichloro-1,1,1,4,4,4-hexafluoro-2-butene[a]
Enflurane			
1	86	95	Chlorodifluoromethane[c]
2	102	54	1,1,2,2-Tetrafluoroethane[d]
3	102	93	Dichlorofluoromethane[c]
4	117	79	*N*,*N*-Dimethyl-2-ethoxyethylamine[b]
5	118	91	Chloroform[c,d]
6	182	54	2-Chloro-1-(chlorometoxy)-1,1,2-trifluoroethane[d]
Isoflurane			
1	182	54	2-Chloro-1-(chlorometoxy)-1,1,2-trifluoroethane[a]
2	136	68	1-Chloro-1,1,2,2-tetrafluoroethane[d]
3	152	88	2,2-Dichloro-1,1,1-trifluoroethane[b]
4	102	54	1,1,2,2-Tetrafluoroethane[d]
5	118	91	Chloroform[c]

[a] 600 °C in glass.
[b] 500 °C in stainless steel.
[c] 400 °C in aluminium.
[d] 500 °C in copper.

ion either directly or indirectly in the ionisation process. The relative abundance of the fragments produced is related to the strength and the chemical nature of the bonds that held the fragments to the rest of the molecules and shows the likely break up points. Therefore, we only need to consider the most abundant, the base peak and the other major peaks appearing in the spectra. Predicting the identity of the mass spectroscopic fragments may help to explain the formation of the suggested products that were later obtained in the experimental decomposition process. The isotope effect may help to confirm the predicted fragments actually present in the spectra by comparing peak sizes.

Molecules containing heavy isotopes will show up peaks at m/e one or more units higher than normal; thus, there will be small peaks at $M+1$ and $M+2$. The relative abundance of heavy isotopes are well known and since the heavy isotopes occur in definite proportions, the probability of finding one or more in a given molecule can be calculated; thus, we can predict the height of the $M+1$ or $M+2$ peaks relative to the parent peak. The appearance of the mass spectrum of a halogen containing compound is profoundly affected by the number of halogen atoms present since isotopic abundance and the fragmentation of mixed halogen compounds are very complicated, fluorine, being mono-isotopic, presents no problem in this respect. Halothane, one of the volatile anaesthetics, studied is an example of such compounds that includes three halogen atoms. The other anaesthetics, isoflurane,



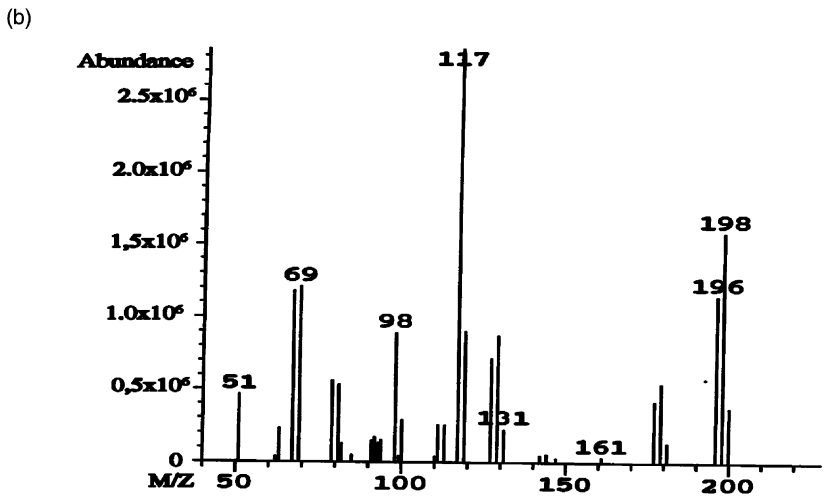


Fig. 1. Isotopic abundances for Br and Cl atoms and probability of the peak heights for halothane (or any fragment) including these isotopes (a). Mass spectrum of halothane (b).

and enflurane, including no Br, give relatively simple fragmentation patterns. The relative abundance and atomic weights of bromine and chlorine and, molecular weights for halothane with different isotopes and probability of peak heights relative to the parent peak are given in Fig. 1. It may be said that (a) three peaks in a 3:4:1 ratio at M, $M+2$ and $M+4$ for different isotope combinations show that the fragment molecule includes Cl and Br atoms together, (b) two equal peaks in a 1:1 ratio at M and $M+2$ shows that Cl is excluded and Br exists in the fragment molecule, (c) two peaks in a 3:1 ratio at M and $M+2$ shows that Br is excluded and Cl exists in the fragment molecule (this is also valid for the products of enflurane and

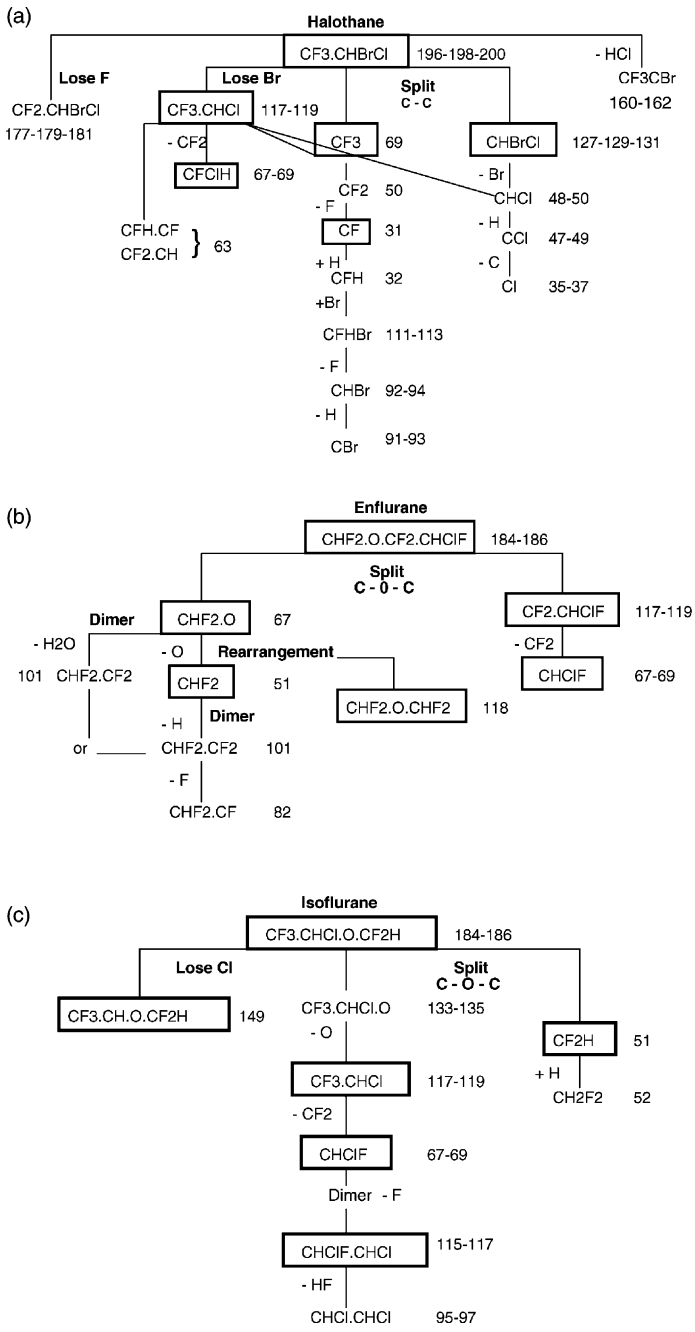
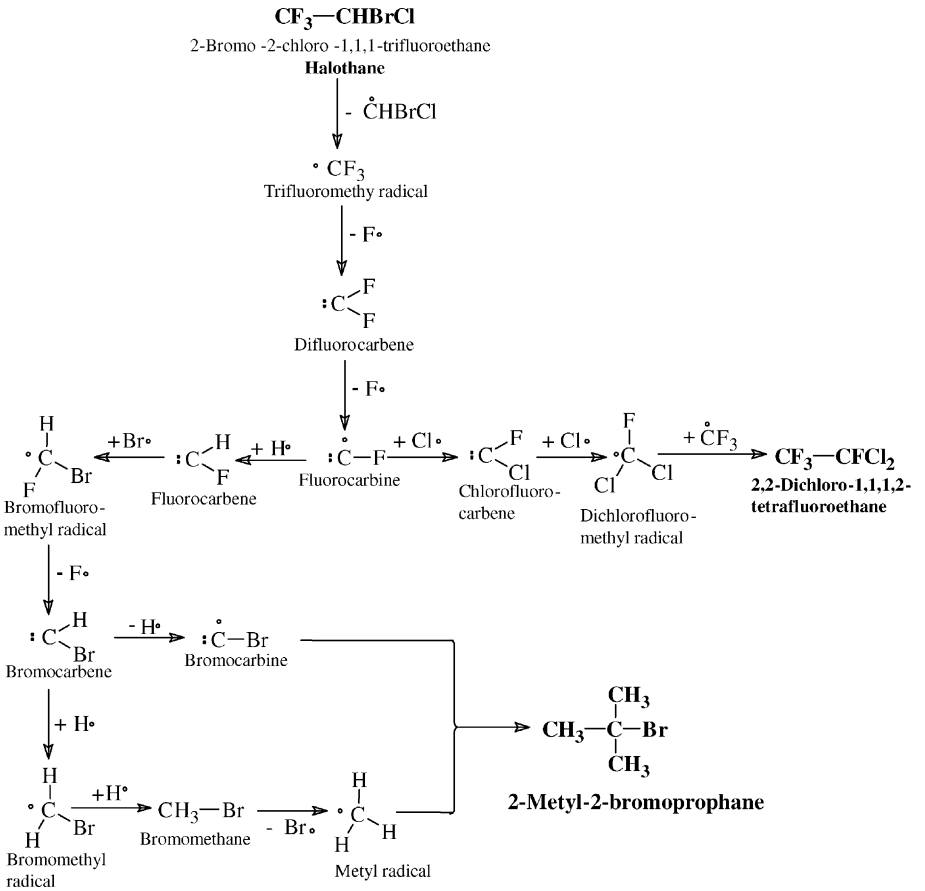


Fig. 2. The possible mass spectrometric fragmentation pattern occurring in the ionisation process for halothane (a), enflurane (b) and isoflurane (c).

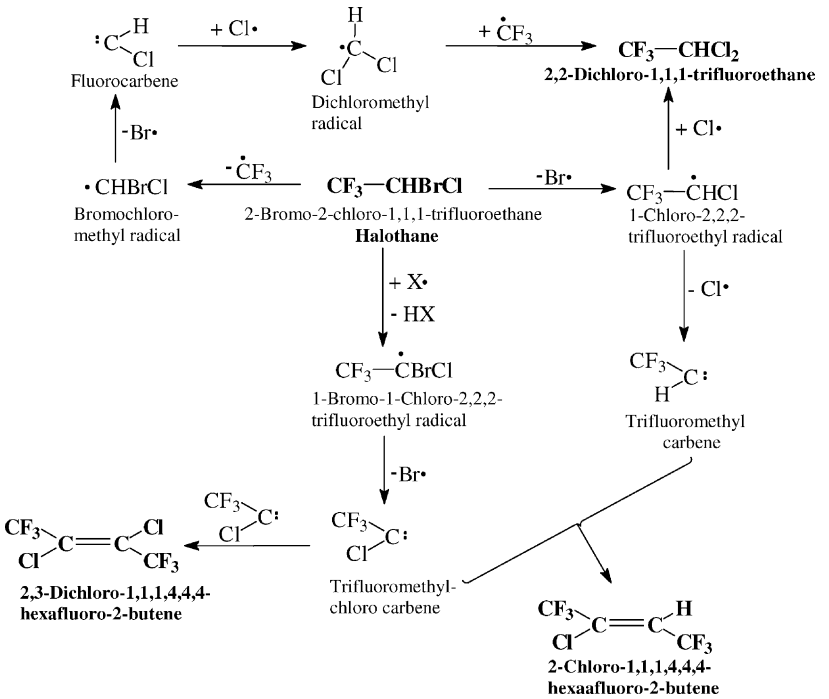
isoflurane molecules), (d) only one peak at *M* shows that Br and Cl are excluded together and only F exists in the fragment molecule (F is mono-isotopic). It should be borne in mind that these figures exclude any contribution from 13C and 2H isotopes in the fragment molecules.

In the light of isotopic probability information, the possible fragments (improbable fragments have too low abundances to be observed) appear in the mass spectrum of anaesthetics were predicted and arranged as a cluster by the help of molecular weights and isotope patterns of fragments. These clusters are given for each anaesthetic molecule in Fig. 2a–c. The encircled fragments in each cluster were the most abundant ones in the mass spectrum and indicate the likely points in the breaking up of the anaesthetic molecules. The numbers, given beside the fragments, are the molecular weights (or *m*/*z* values) varying with the probability of the isotopes present in the molecules.

In Schemes 1 and 2, possible fragmentation of halothane into radicals and then forming the identified major decomposition products (see Table 1) in thermal process have been



Scheme 1. Possible decomposition pathway of halothane molecule to form the observed products by using ionisation fragments.

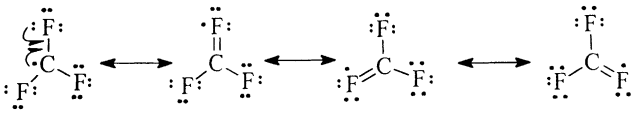


Scheme 2. Possible decomposition pathway of halothane molecule to form the observed products by using ionisation fragments.

predicted. According to Schemes 1 and 2, the fragments of halothane observed in the ionisation process at $m/e = 177, 179, 181$ for $CF_2CHBrCl$; $m/e = 127, 129, 131$ for CHBrCl; $m/e = 160, 162$ for CF_3CBr; $m/e = 117, 119$ for CF_3CHCl; $m/e = 67, 69$ for CFClH; and $m/e = 63$ for CFHCF or CF_2CH may not be formed in the furnace, a metal/metal oxide catalysed thermal decomposition seems possible for no stable product formation is likely possible from the unstable fragments given above. As shown in Scheme 1, bromomethane that acts in the forming of 2-methyl-2-bromopropane and 2,2-dimethyl-1-bromopropane and later decomposes to form 2-methyl-2-bromopropane and 2,2-dimethyl-1-bromopropane is not among the stable fragments in the ionisation process. In addition to this, absence of the products (e.g. 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene), which are possibly formed by the dimerisation of radicals, may show that whether their abundances are very low or their concentrations are insufficient for dimerisation.

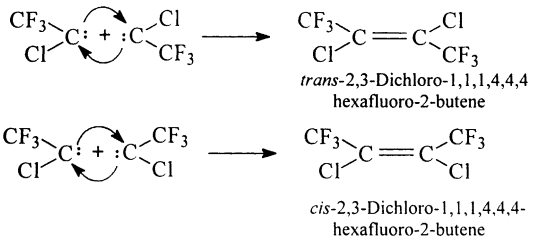
The bonding energies of halothane molecule imply that (C–Br = 58 kcal/mol, C–Cl = 81 kcal/mol, C–C = 83 kcal/mol, C–H = 99 kcal/mol, C–F = 117 kcal/mol) C–Br bond is the most fragile point for the thermal decomposition. The formation mechanism of 2-chloro-1,1,1,4,4,4-hexaflouro-2-butene in Scheme 2 is therefore based on this sort of decomposition. But the other halogenated products observed do not seem to follow the same pathway showing that bond strength is not the principal parameter for the decomposition process of the molecule. All the other compounds are however formed by the reactions including a C–C bond splitting with the exception of 2-chloro-1,1,1,4,4,4-hexafluoro-2-butene

and 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene. This strongly indicates that stabilities of the radicals are very effective in the formation mechanisms of the observed compounds. The stability of trifluoromethyl radical which is formed by splitting of C–C bond is higher than the stability of 1-chloro-2,2,2-trifluoroethyl radicals which is formed by decomposition of C–Br bond during 2-chloro-1,1,1,4,4,4,-hexafluoro-2-butene formation and 1-bromo-1-chloro-2,2,2-trifluoroethyl radical which is formed in 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene formation. Fluorine atom gives stronger resonance with the same period element of carbon compared to other halogen atoms and this causes a stability increase. However, in ethyl radicals given above, due to –I effect of CF_3 group and because chlorine and bromine are third- and fourth-period elements, they overlap weakly with carbon atom and causes these radicals to be less stable than CF_3 radicals:

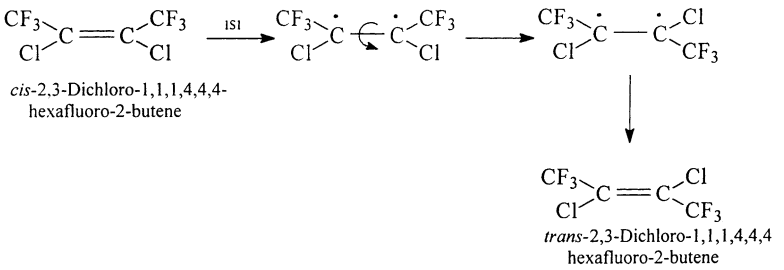


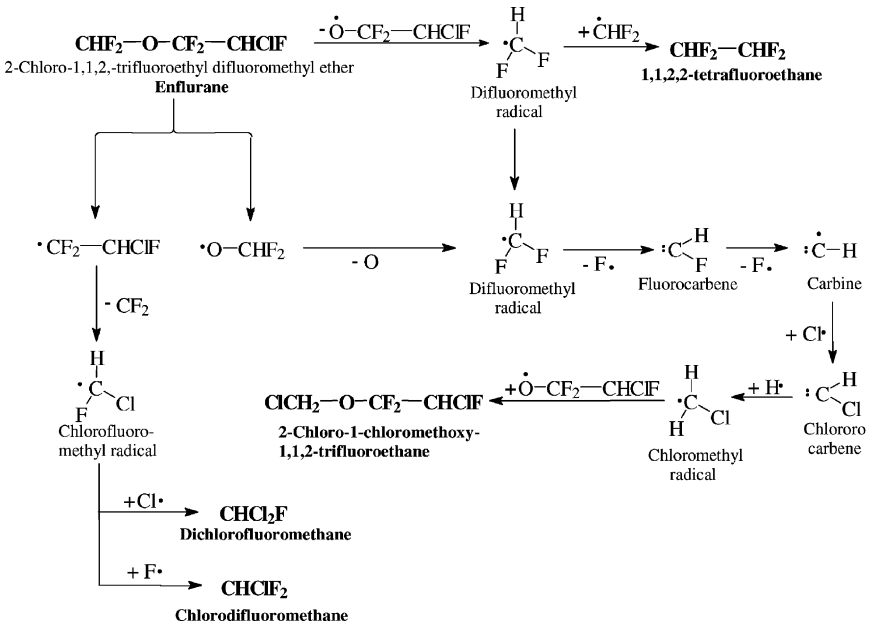
Formation of 2-chloro-1,1,1,4,4,4-hexafluoro-2-butene via a less stable radical indicates that the weakness of the bond allows this type of cracking, despite the radical is less stable.

The products, 2-chloro-1,1,1,4,4,4-hexafluoro-2-butene and 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene are thought to be formed by a carbon dimerisation reaction. Approaching of carbons for dimerisation determines the geometries of the new compounds:



Formation of both the dimerisation products given above seems theoretically possible in the reaction. Since approaching of CF_3 groups on the same plane seems more difficult and the groups have to be on the same plane on complement of the formation of *cis* molecule structure is less stable form. In contrast to *cis* compound, low repulsive forces between the groups increases the chance of the formation of *trans* compound. Despite the fact that the *cis* structured molecule may be formed, but π-bond, which has approximately 63 kcal/mol energy may be broken to give more stable *trans* product by the effect of heat:



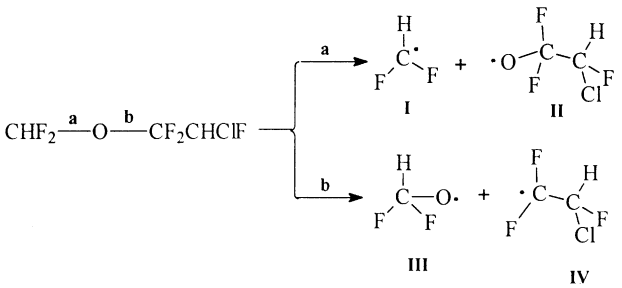


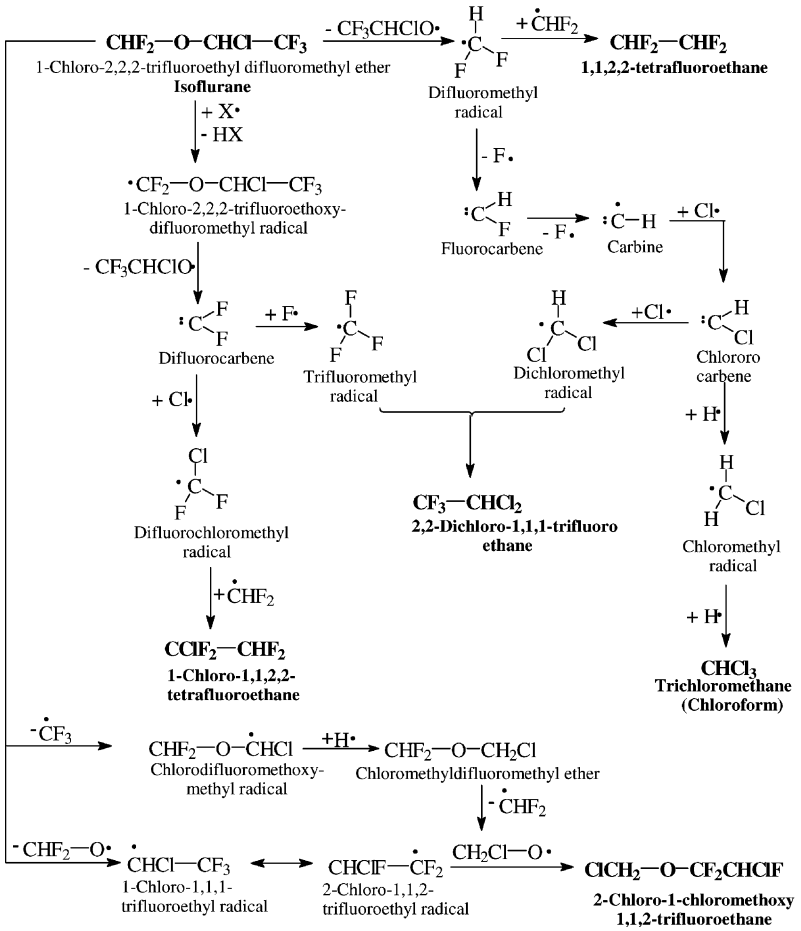
Scheme 3. Possible decomposition pathway of enflurane molecule to form the observed products by using ionisation fragments.

When Scheme 3, which shows the formation of the stable compounds by the effect of thermal and catalytic decomposition, and Fig. 2b, which shows the decomposition fragments in the ionisation process, are compared, some remarkable differences may be observed as in halothane decomposition. One of the differences is the absence of $m/e = 118$ CHF_2–O–CHF_2 among the stable products of the thermal and catalytic decomposition process. Absence of CHF_2–O–CHF_2 may show that thermal decomposition of enflurane is likely the result of fragmentation of the C–O bonds:

$$CHF_2\overset{a}{-}O\overset{b}{-}CF_2CHClF$$

The 'a' and 'b' bonds in CHF_2–O–CF_2CHClF molecule have approximately equal strength and therefore, which of this bond would be broken depends on the stability of the formed radicals. The stabilities of the radicals severely affect the progress of the reaction:





Scheme 4. Possible decomposition pathway of isoflurane molecule to form the observed products by using ionisation fragments.

The stabilities of the carbon centred radicals are compared in the above scheme. Radical I is more stable than radical IV. Since both radicals have two –F atoms belonging to radical centre, the stability of radicals I and IV hence depends on –H and –CHClF groups. The –I effect of halogen atoms in –CHClF groups makes radical IV less stable compared to radical I. If the stabilities of the oxygen centred radicals are compared, radical III is found more stable than the others for the same reasons. But, in this case, –CHClF group is less effective due to the distance to radical centre and therefore the decomposition likely occurs via ‘a’ bond. Despite this point, ‘b’ bond seems to be decomposed in aluminium in the experiments.

Decomposition pathway of isoflurane corresponds to enflurane molecule. Equally strengthen C–O bonds are broken to form stable radicals in the reaction. Fracturing of ‘a’ bond

in the isoflurane molecule primarily leads to form the observed decomposition products:

$$CHF_2\overset{a}{-}O\overset{b}{-}CHClF_3$$

As it may be seen from Scheme 4 that while products originated from the both broken C–O bonds contributes the formation of 2,2-dichloro-1,1,1-trifluoroethane, the products such as 1-chloro-1,1,2,2-tetrafluoroethane, 1,1,2,2-tetrafluoroethane and chloroform are mainly composed by the fractured 'a' bond products. But, 1-chlorometoxy-2-chloro-1,1,2-trifluoroethane is likely formed via more stable CF_2–CHClF radical which was originated from the CF_3–CHCl radical of the fractured 'b' bond. Because isoflurane (like halothane) has a suitable structure to produce CF_3 radical which is more stable compared to other halogenated ones, the C–C bond splitting is likely to occur in the formation of 1-chlorometoxy-2-chloro-1,1,2-trifluoroethane in isoflurane molecule. Absence of the $CH_2ClOCHF_2$ compound among the stable products which forms in the production of 2-chloro-1-(chlorometoxy)-1,1,2-trifluoroethane process indicates that this compound is completely destroyed in the reaction. In addition to this, no stable decomposition product have been predicted via fragment occurred at $m/e = 149$ $CF_3CH_2OCHF_2$ (1-(difluorometoxy)-2,2,2-trifluoroethyl) observed in the mass spectrometric ionisation process. This may show that the thermal decomposition of isoflurane into this product is not very similar to the ionisation mechanism.

No oxygen-containing compound, except enflurane and isoflurane having oxygen in their etheric structures is determined in the thermal decomposition process. This may imply that oxygen or nitrous oxide in the carrier gas may not directly take part in the thermal decomposition mechanisms. Observed one nitrogen-carrying compound with enflurane in stainless steel and absence of any similar compound with isoflurane may indicate an incorrect identity regarding with this compound.

4. Conclusion

The analytical investigation of the decomposition pathway of anaesthetics shows that the major decomposition products (see Table 1) may be reproduced by using the ionisation fragments of each anaesthetics molecule. This may also indicate that mass spectrophotometric ionisation and thermal decomposition pathway of investigated anaesthetics somewhat resemble each other, but one cannot conclude that two decomposition processes are completely similar. On the other hand, SI values of suggested decomposition products may not be used as an actual indicator of the molecular similarities for the identified molecules. In the literature, there is a lack of the available data on the thermal and metal/metal oxide involved decomposition mechanism and products of halogenated anaesthetics and therefore no standard was available for conclusive identification of the observed products. However, there is a room to develop the available information. For example, the percentage of the thermal decomposition, kinetic of the formation reactions; toxicity of the formed halogenated products may further be studied. A better approach would involve combining the GC–MS in a series of the experimental system, employing a reaction column filled with metal chips for efficient and reliable evaluations with lighter and inorganic components. But this approach

has serious drawbacks since corrosion of the metal parts is one of the main problems. It is believed that the present study fills the gap in the field and gives basic information for further toxicological studies. The results here clearly show that mass spectrophotometric ionisation processes and furnace decomposition processes for the investigated anaesthetics are somewhat similar in many respects.

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