One-electron Reduction of Halothane (2-Bromo-2-chloro-1,1,1-trifluoroethane) by Free Radicals. Radiation Chemical Model System for Reductive Metabolism

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The reaction mechanism of one-electron and radical-induced degradation of the general anaesthetic halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) has been investigated for γ-irradiated, oxygen-free aqueous solutions containing various alcohols or formate. Modern ion chromatography and conventional g.c.–m.s. methods were used as analytical tools for identification of end products. This includes quantitative determination of Cl^- ions in the presence of Br^- ions. Reduction of halothane by hydrated electrons, various alcohol radicals, and $\dot{C}O_2^-$ proceeds *via* Br^- elimination and $CF_3\dot{C}HCl$ radical formation as initial step. t-Butyl alcohol radicals $\dot{C}H_2C(CH_3)_2OH$ abstract bromine atoms to yield $BrCH_2C(CH_3)_2OH$ which suffers base-catalysed Br^- elimination. Chain reactions leading to high Br^- yields are observed in solutions containing propan-2-ol, ethanol, methanol, and formate. Based on $2k = 10^9$ mol^{-1} dm^3 s^{-1} for the dimerization of 2 $CF_3\dot{C}HCl$ radicals the following rate constants have been measured: $k(CF_3\dot{C}HCl$ + propan-2-ol) = 670 mol^{-1} dm^3 s^{-1}, $k(CF_3\dot{C}HCl$ + ethanol) = 130 mol^{-1} dm^3 s^{-1}, $k(CF_3\dot{C}HCl$ + methanol) = 27 mol^{-1} dm^3 s^{-1} and $k(CF_3\dot{C}HCl$ + formate) = 2 900 mol^{-1} dm^3 s^{-1} Dimerization of $CF_3\dot{C}HCl$ leads to $CF_3CHClCHClCF_3$ which suffers base-catalysed HCl elimination to yield the two stereoisomers of $CF_3CH{=}CClCF_3$. The halothane results are compared with corresponding findings in CCl_4-containing systems.

The chemistry of the free radicals that are derived from the general anaesthetic halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) has recently aroused much interest.[1-4] These radical species are highly reactive and are believed to play a significant role in the metabolism of halothane.[5] Different product patterns have been found in biological systems, depending on the oxygen concentration of the environment,[6-12] and consequently a distinction was made between an aerobic and an anaerobic metabolism. Details on this subject as well as on the different observed products are comprehensively documented in the literature.[13]

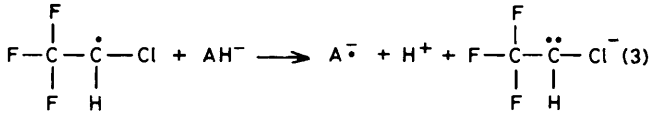
It is now fairly well established that free radicals are indeed formed during the anaerobic metabolism of halothane.[14,15] In the primary step one-electron transfer from the cytochrome P-450 enzyme system, which is located mainly in the endoplasmic reticulum in liver cells, to halothane leads to the formation of bromide ions and 2-chloro-1,1,1-trifluoroethyl radicals [reaction (1)]. The $CF_3\dot{C}HCl$ radical has unambiguously been identified by e.s.r. and other methods in living cells under hypoxic conditions.[15-18]

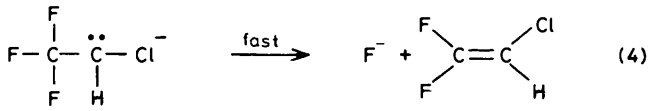
$$e^- + CF_3CHBrCl \longrightarrow Br^- + CF_3\dot{C}HCl \qquad (1)$$

Whether free radicals are metabolically formed also under normal concentrations of oxygen (normoxic conditions) remains equivocal. This question is of interest since O_2 is an efficient substrate for electron uptake in the cytochrome P-450 enzyme system. In addition any $CF_3\dot{C}HCl$ could add oxygen *via* reaction (2). This process has been shown by time-resolved pulse radiolysis techniques to occur with a high rate constant of k_2 1.3 × 10^9 mol^{-1} dm^3 s^{-1}.[3] Attempts to trap such peroxyl radical species *in vivo* have however failed so far for $CF_3CHClO_2^{\bullet}$[15] and the related $CCl_3O_2^{\bullet}$.[19,20]

$$CF_3\dot{C}HCl + O_2 \longrightarrow CF_3CHClO_2^{\bullet} \qquad (2)$$

An elegant way to produce $CF_3\dot{C}HCl$ radicals and to study their reactions is by means of radiation chemical methods. In aqueous solution one-electron reduction of halothane by hydrated electrons occurs according to equation (1). In a recent





(4)

paper we reported on the free-radical-mediated elimination of F^- ions which occurs however only under anaerobic conditions and in the presence of additional substrates with suitable redox properties like ascorbate (AH^-).[2] The underlying chemistry is based on a further reduction of the $CF_3\dot{C}HCl$ radical and immediate rearrangement of the carbanion thus formed *via* release of a fluoride ion and formation of 2-chloro-1,1-difluoroethene. A remarkable aspect is that both F^- and $CF_2{=}CHCl$ are also formed if halothane is degraded metabolically under hypoxic conditions.[9,10,12]

In the present study we investigated the reaction of halothane with radicals derived from various alcohols in aqueous solutions under anaerobic conditions. Irradiation of dilute alcohol solutions primarily produces hydrated electrons, e_{aq}^-, and $^{\bullet}OH$ radicals in about equal yields of G 2.8 species per 100 eV absorbed energy (*ca.* 0.3 μmol per J), and also $H^{\bullet}$ atoms but only at a much lower yield of G 0.6 (or 0.06 μmol per J absorbed energy). Hydrated electrons can easily be converted into $^{\bullet}OH$ radicals *via* reaction (5) leaving essentially only $^{\bullet}OH$ and $H^{\bullet}$ in a *ca.* 10:1 ratio. These radicals abstract hydrogen atoms from the alcohols, preferentially from the carbon atom in the α-position to the hydroxy group [reaction (6)].[21] The resulting α-hydroxyalkyl radicals usually exhibit good reducing properties, *i.e.* are potential reducing agents towards halothane. β-Hydroxyalkyl radicals, which are formed for example in the reaction of $^{\bullet}OH$ with t-butyl alcohol [reaction (7)], are, on the other hand, much poorer reductants and are generally inert with

respect to redox processes. These radicals may however undergo abstraction reactions, *i.e.* could serve as a general probe for such processes with halothane.

$$e_{aq}^- + N_2O \longrightarrow N_2 + OH^- + {}^{\bullet}OH \quad (5)$$

$$^{\bullet}OH/H^{\bullet} + RC(R')HOH \longrightarrow H_2O/H_2 + R\dot{C}(R')OH \quad (6)$$

$$^{\bullet}OH + CH_3C(CH_3)_2OH \longrightarrow H_2O + {}^{\bullet}CH_2C(CH_3)_2OH \quad (7)$$

Experimental

All compounds used were of highest commercially available purity. Halothane (Höchst; with 0.01% thymol) was used as received. All other substances were from Merck and used without further purification. Solutions were generally prepared in 500 cm^3 glass vessels, which could be sealed gas-tight by septa. Oxygen was removed by passing nitrogen (Linde; $[O_2] < 3 \times 10^{-4}$ vol %) through the solutions for about 1 h. Whenever hydrated electrons were to be converted into $^{\bullet}OH$ radicals, the solutions were saturated with N_2O (Höchst) which was passed through an 'Oxisorb' (Messer Griesheim) column containing a catalyst to remove any possible traces of oxygen. The alcohols were usually saturated with the respective gas separately prior to introduction into the solutions through a septum. The highly volatile halothane was injected as received, *i.e.* not deoxygenated; since the absolute amount (*ca.* 40 μl in 400 ml solution) of halothane was always very small the concentration of oxygen introduced into the solution by this procedure remained negligible.

The solutions were irradiated in the field of a ^{60}Co γ-source with an applied dose-rate of *ca.* 300 Gy h^{-1} over the period of investigations. The actual accurate dose rates were always determined by normal Fricke dosimetry [taking $G(Fe^{3+}) = 15.6$ in air-saturated solutions].[22]

Ionic products were determined by means of high-performance ion chromatography h.p.i.c.[23] The apparatus used was a DIONEX 2010i equipped with a separator column AS 4 (50 cm length) and conductivity detection. A solution of 2.8×10^{-3} mol dm^{-3} $NaHCO_3$ and 2.24×10^{-3} mol dm^{-3} Na_2CO_3 was used as eluant with a flow rate of 2 cm^3 min^{-1}. After the separator column the solution was passed through a fibre suppressor, where Na^+ ions of the eluant were irreversibly replaced by H^+ ions *via* exchange through a cation-permeable membrane. The presence of protons now affects the equilibria (8) and (9) in such a way (shift to the right-hand sides) that the eluant conductivity is drastically reduced. The remaining background conductivity is finally set off electronically. The so-called 'water-dip', which is inherent to h.p.i.c. and which shows up in the chromatograms as a big negative peak, was removed by passing the electric signal from the detector through an interface, where only positive electric signals could pass before feeding it into the integrator. It was therefore possible to measure at an extremely high sensitivity (full scale corresponded to 3 μS conductivity) without overloading the integrator with the negative water-dip signal.

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \quad (8)$$

$$2H^+ + CO_3^{2-} \rightleftharpoons H_2CO_3 \quad (9)$$

The lower detection limits were 1×10^{-6} and 2×10^{-6} mol dm^{-3} for Cl^- and Br^-, respectively. Calibrations were done daily by using non-irradiated solutions which contained known amounts of Cl^- and Br^-. The sensitivity for the detection of chloride depends markedly on the matrix, because Cl^- elutes in the tailing of the water-dip, whereas Br^- determination is almost independent of the various matrices.

Peak areas were integrated with a Shimadzu C-R1B or a Spectra-Physics Autolab 1.

Gas chromatographic analysis was performed with a Varian 3700 equipped with a 6 ft Porapak-P separation column. Helium (Linde) was used as eluant with a flow rate of 21 cm^3 min^{-1} at 100 °C. The injector temperature was 150 °C. Identification of the peaks was achieved with a quadrupole mass spectrometer MAT 44 using electron impact ionization. The acceleration voltage was 70 V and the emission current 0.8 mA. The mass spectrometer was coupled on line with the gas chromatograph.

The water used throughout this study was deionized and filtered in a 'Millipore-system' and corresponded in quality to triply quartz-distilled water. Its specific resistance was always between (5—18) $\times 10^6$ Ω^{-1} cm. All experiments were carried out at room temperature.

Experimental error limits are estimated to ± 10% for the radiation chemical data and ± 2% for the chromatography measurements.

Results and Discussion

(1) *Solutions containing t-Butyl Alcohol.*—In a previous paper[2] we reported that reduction (10) of halothane by hydrated electrons in neutral solution yields bromide ions with a final G value of $G(Br^-) = G(e_{aq}^-) = 2.8$ (~ 0.28 μmol per J absorbed dose) using an ion-sensitive electrode as the analytical tool. With this technique it was not possible to measure the chloride yields, as well, since determination of Cl^- with ion-sensitive electrodes cannot be done in the presence of Br^- ions. Chloride ions may however be expected as one of the products from consecutive reactions of the $CF_3\dot{C}HCl$ radical. We therefore investigated this system again using ion chromatography as the analytical tool.

$$e_{aq}^- + CF_3CHBrCl \longrightarrow Br^- + CF_3\dot{C}HCl \quad (10)$$

Ion chromatograms of γ-irradiated oxygen-free solutions containing 1×10^{-3} mol dm^{-3} halothane and 1% (v/v) t-butyl alcohol, which had been irradiated at different pH values, are shown in Figure 1. In all solutions, both Br^- and Cl^- peaks are to be seen, *i.e.* chloride ions are indeed eliminated during the reaction process. The big peak in the middle chromatogram (Figure 1b) stems from 5×10^{-4} mol dm^{-3} phosphate buffer, which was added to the solution to keep the pH constant during the irradiation. Concentration *versus* dose plots with at least four measured points gave excellent straight lines for both the Br^- and Cl^- yields. (The total absorbed doses were in all cases small enough to keep the total conversion of halothane well below 10%.) The respective G values are listed in Table 1.

Most surprisingly, the yield of Br^- ions was found to be considerably higher than that measured previously by an ion-sensitive electrode. This means that the Br^- yield now exceeds the yield of hydrated electrons initially produced. A chain reaction can, however, be ruled out since no dependence on dose rate was observed. Furthermore, the Br^- and Cl^- yields seem to depend on the pH of the irradiated solutions, being lowest for the neutral pH range. All these seemingly conflicting results can be rationalized in terms of distinct chemical reactions as shall be discussed in the following.

A closer look at the chromatograms shown in Figure 1 reveals that the shapes of the peaks, particularly the encircled bottom sections, are not identical, as would be expected from chromatographic theory. 'Normal' sharp peaks were only obtained from solutions, which had been irradiated at basic pH (Figure 1c). In the other two chromatograms (Figures 1a, b) the

Table 1. Yields of bromide and chloride ion formation (expressed in G values) in the radiolysis of oxygen-free solutions of 1×10^{-3} mol dm^{-3} halothane and 1% (v/v) t-butyl alcohol at different pH values.

pH value	Gas	Buffer ($H_2PO_4^-$–HPO_4^{2-})	$G(Br^-)$	$G(Cl^-)$
2.2	N_2		4.09	1.57
4.0	N_2		4.00	2.20
5.0	N_2	5×10^{-4} mol dm^{-3}	3.40	2.00
6.5	N_2	5×10^{-4} mol dm^{-3}	3.40	1.64
8.1	N_2	5×10^{-4} mol dm^{-3}	3.69	1.69
10.0	N_2		5.25	2.60
5.0[b]	N_2O[a]	5×10^{-4} mol dm^{-3}	1.35	1.23
5.0[c]	N_2O[a]	5×10^{-4} mol dm^{-3}	4.70	0.3
11.0	N_2O[a]		4.66	not measured

[a] In N_2O-saturated solutions 94% of the hydrated electrons are converted into $^{\cdot}CH_2C(CH_3)_2OH$ radicals under these conditions. [reactions (5) and (7)]. [b] Analysed directly after irradiation without further processing. [c] Irradiated solution was flushed with nitrogen, then brought to pH 10, and then analysed (for explanation see text).

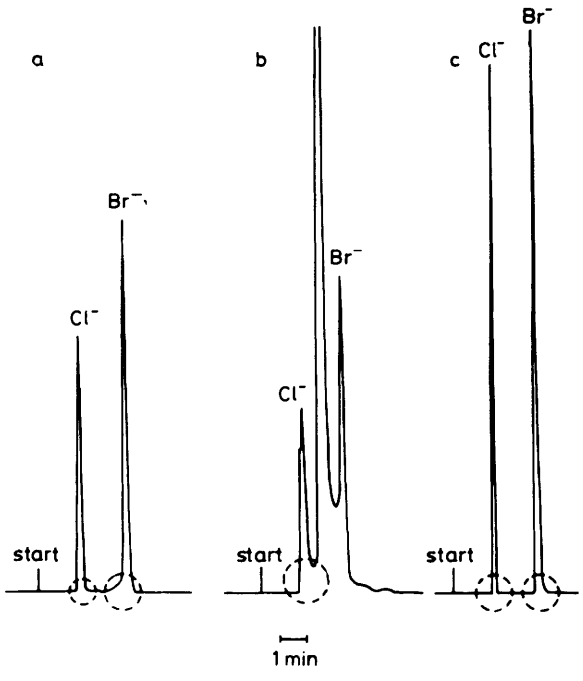


Figure 1. Ion-chromatograms of nitrogen-saturated solutions containing 1×10^{-3} mol dm^{-3} halothane and 1% (v/v) t-butyl alcohol: a, irradiated at pH 4; b, irradiated at pH 8.1 and c, irradiated at pH 10. The absorbed dose was in all cases 100 Gy

Br^- and Cl^- peaks are much broader at the base and additionally show fronting and tailing effects. It is important to note that this behaviour is restricted to irradiated solutions only. Ion chromatographic analysis of non-irradiated acidic solutions shows sharp peaks, as in Figure 1c, and no sign of abnormalities.

The following points are important for the understanding of these effects. (1) The solutions were always injected into the chromatograph directly after γ-irradiation without further processing; (2) the eluant for the separation is basic (pH *ca.* 9.5); and (3) only free ions are detectable in the conductivity cell of the ion chromatograph. Hence, the non-ideal chromatographic behaviour could plausibly be explained by a base-catalysed decay of one or more radiation products in the column. Thus, after the injection of the sample, additional Cl^- and Br^- are formed during the chromatographic separation procedures. Since the generation of these additional ions is a function of time this must necessarily result in a spectrum of retention times, and consequently in peak broadening. Only if the irradiations had been undertaken in basic solution would these decay processes have already occurred during the irradiation period. These considerations are supported by the fact that the highest yields of Cl^- and Br^- were indeed obtained in irradiated basic solutions.

The bromide ion yield in basic solutions of $G(Br^-)$ 5.25 amounts to close to the total yield of primary radicals from water radiolysis, *i.e.* $G(Br^-) \cong G(e_{aq}^-) + G(H^{\cdot}) + G(^{\cdot}OH)$. Since $^{\cdot}OH$ radicals and presumably also $H^{\cdot}$ atoms were removed by the t-butyl alcohol in the solution C [reactions (5) and (7a)] the results suggest that not only e_{aq}^- but also $^{\cdot}CH_2C(CH_3)_2OH$ radicals contribute to the overall bromide yield. We suggest that an abstraction reaction (11) followed by a base-catalysed solvolysis (12) is responsible for the additional bromide yield. Evidence for this reaction sequence was obtained from irradiated solutions containing 1% (v/v) t-butyl alcohol and 1×10^{-3} mol dm^{-3} halothane at pH 11 under N_2O. Under these conditions more than 94% of the e_{aq}^- are converted into $^{\cdot}OH$, and therefore $^{\cdot}CH_2C(CH_3)_2OH$ is essentially the only radical species available for reaction with halothane. In this system bromide ions were produced with a yield of $G(Br^-)$ 4.7. This high yield clearly demonstrates the involvement of the t-butyl alcohol radicals.

$$^{\cdot}OH/H^{\cdot} + CH_3C(CH_3)_2OH \longrightarrow {}^{\cdot}CH_2C(CH_3)_2OH + H_2O/H_2 \quad (7a)$$

$$^{\cdot}CH_2C(CH_3)_2OH + CF_3CHBrCl \longrightarrow BrCH_2C(CH_3)_2OH + \text{products} \quad (11)$$

$$BrCH_2C(CH_3)_2OH \xrightarrow[\text{base}]{} Br^- + HOCH_2C(CH_3)_2OH \quad (12)$$

Figure 2 shows chromatograms of the same N_2O-saturated solutions at pH 5 (buffered with 5×10^{-4} mol dm^{-3} $H_2PO_4^-$) which were irradiated under identical conditions but processed afterwards in different ways. Direct injection of the irradiated solution again yields the non-ideal chromatogram (Figure 2a) similar to that presented in Figure 1b. Chromatogram 2b refers to a sample which had been made basic by addition of a 1 mol dm^{-3} HCO_3^-–CO_3^{2-} solution (2 ml) after irradiation but prior to injection into the ion chromatograph. Sharp peaks are now to be seen because all base-catalysed decay processes could occur before the analysis. Also much higher yields of Br^- and Cl^- were obtained. Sample 2c had been flushed with nitrogen for 30 min directly after the irradiation to remove all volatile compounds (including halothane). Afterwards the solution was also made basic prior to analysis. Again, normal sharp chromatographic peaks appeared, but more important almost no chloride could be detected anymore while comparison with Figure 2b reveals that the bromide yield remained unaffected. These experiments clearly indicate that both chloride and bromide ions are formed by base-catalysed processes, but are likely to result from different precursors. In particular, these observations provide the rationale for the different Br^- and Cl^- ion yields measured in solutions which were irradiated at the various pH values (Table 1). Except for the high-pH solution they are not a quantitative measure for the radical-induced processes, but rather reflect the extent of solvolysis of products before and during the ion chromatographic procedure.

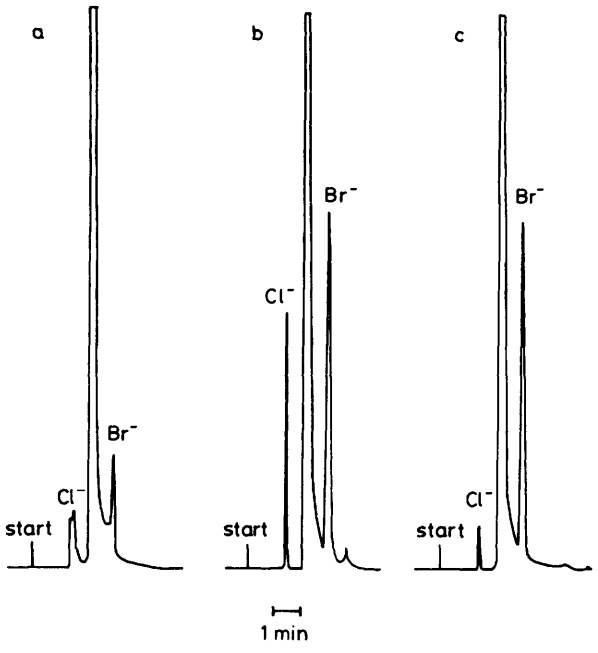


Figure 2. Ion-chromatograms of N_2O-saturated solutions containing 1×10^{-3} mol dm^{-3} halothane and 1% (v/v) t-butyl alcohol irradiated at pH 5 (buffered with 5×10^{-4} mol dm^{-3} phosphate). The dose was always 50 Gy. The solutions were processed differently after the irradiation (see text)

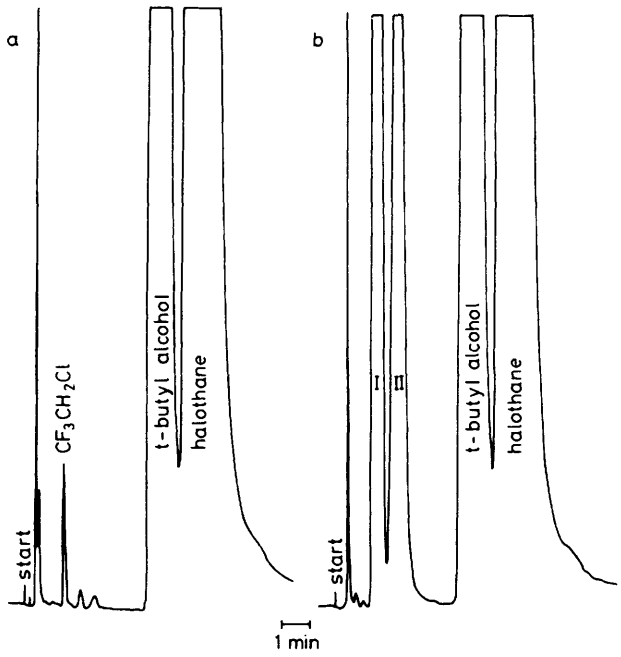


Figure 3. Gas chromatographic analysis of the head-space gases of irradiated solutions containing 1×10^{-3} mol dm^{-3} halothane and 1% (v/v) t-butyl alcohol at pH 4 (absorbed dose 49.7 Gy): a, analysis was performed immediately after irradiation; b, prior to analysis the solution was adjusted to pH 9.5. Sensitivity range: 10^{-11} A mv^{-1}

2-Bromomethylpropan-2-ol formed *via* reaction (11) is not expected to be volatile owing to its hydrophilic hydroxy substituent. All these considerations provide the explanation for the relatively low yield of $G(Br^-) = G(e_{aq}^-) = 2.8$ measured in irradiated neutral or slightly acidic solutions using the ion-sensitive electrode. Under these pH conditions 2-bromomethylpropan-2-ol is still stable with respect to solvolysis and the Br^- yield accounts only for the initial dissociative electron capture by halothane [reaction (10)].

The precursor of the Cl^- ions obviously stems from subsequent reactions of $CF_3\dot{C}HCl$ radicals and must also be subject to solvolysis under basic conditions. In addition, it is fairly volatile. Considering that the chloride ion yield at maximum reaches half the Br^- ion yield (see Table 1) we propose radical–radical combination to be the process of interest. In principle, two possibilities, namely combination (13) and disproportionation (14) (ionic or hydrogen-transfer) have to be envisaged. The ionic pathway (14a) can, however, immediately be excluded since carbanion formation has been shown to result in F^- elimination,[2] which is not observed in our system.

$$CF_3\dot{C}HCl + CF_3\dot{C}HCl \longrightarrow CF_3CHClCHClCF_3 \quad (13)$$

$$CF_3\dot{C}HCl + CF_3\dot{C}HCl \longrightarrow CF_3CHCl^+ + CF_3CHCl^- \quad (14a)$$

$$\longrightarrow CF_3\ddot{C}Cl + CF_3CH_2Cl \quad (14b)$$

Evidence for reaction (13) was obtained by g.c.—m.s. Analysis of the gases from the head space above the irradiated solutions (which should contain at least part of the volatile products) before and after addition of base gave the two gas chromatograms shown in Figure 3. The products were unambiguously identified by their mass spectra and comparison with literature values.[24]

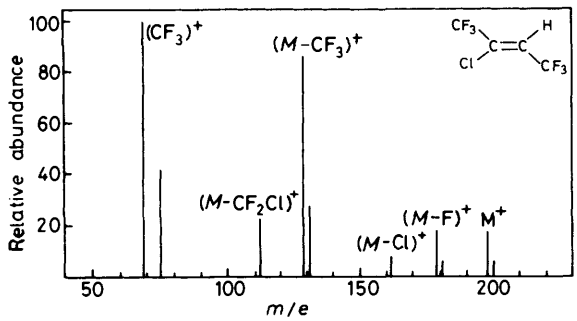
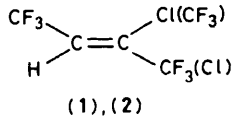


Figure 4. Mass spectrum of the two compounds labelled I and II in the chromatogram shown in Figure 3b

For neutral and acidic solutions only CF_3CH_2Cl is found as reaction product as is shown in Figure 3a. Its yield is however much too small to suggest the disproportionation reaction (14b) as exclusive reaction route (some minor peaks in the chromatogram could not be identified). If the irradiated solutions were treated with base, however, the gas head space contained large yields of two new products labelled I and II in Figure 3b. The masses of these two compounds are absolutely identical and according to their m.s. pattern, which is shown in Figure 4 [base peak at *m/e* 69 (CF_3^+), another strong peak at *m/e* 129/131 $(M-CF_3)^+$, and the molecular peak at *m/e* 198/200 (M^+)], are attributed to the two isomers (**1**) and (**2**). Their formation is taken as conclusive evidence for reaction (13) and



(1), (2)

Table 2. Yields of bromide and chloride ion (expressed as G values) in the radiolysis of nitrogen saturated solutions of 1×10^{-3} mol dm^{-3} halothane at pH 4 and with different concentrations of $^{\bullet}OH$ radical scavengers. For calculations of $k_{18/18a}/\sqrt{2k_{13}}$ and $k_{18/18a}$ (reaction of $CF_3\dot{C}HCl$ radicals with alcohols or formate) see text.

$^{\bullet}OH$ scavenger	Concentration mol dm^{-3}	$G(Br^-)$	$G(Cl^-)$	$\frac{k_{18/18a}}{\sqrt{2k_{13}}}$	$k_{18/18a}$/dm^3 mol^{-1}s^{-1}
$(CH_3)_2CHOH$	2×10^{-2}	13.8	2.8		
	5×10^{-2}	27.6	2.8	2.12×10^{-2}	670
	1×10^{-1}	60.3	3.0		
CH_3CH_2OH	1×10^{-1}	15.9	2.7		
	3×10^{-1}	36.7	2.6	4.1×10^{-3}	130
	5×10^{-1}	51.2	2.85		
CH_3OH	5×10^{-1}	10.5	2.9	8.5×10^{-4}	27
$HCOO^-$	5×10^{-3}	15.0		9.2×10^{-2}	2 900

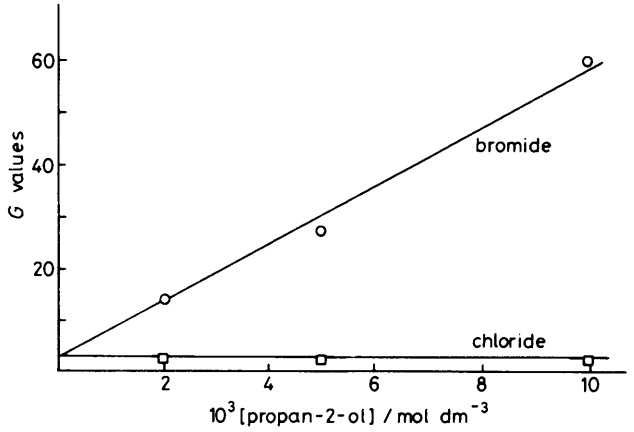


Figure 5. Dependence of the bromide and chloride yields on the propan-2-ol concentration in irradiated nitrogen-saturated solutions of 1×10^{-3} mol dm^{-3} halothane at pH 4

subsequent base-catalysed HCl elimination (15) from the combination product. The identity of the combination product certainly complies with the observed volatility and the overall mechanism presented here explains the 2:1 ratio between Br^- and Cl^- ion yields.

$$CF_3CHClCHClCF_3 \xrightarrow{OH^-} CF_3CH{=}CClCF_3 + HCl \quad (15)$$

From the analytical point of view it would of course have been of interest to assign peaks I and II to a particular stereoisomer. Owing to the lack of original *cis*- and/or *trans*-compounds (with respect to the CF_3 groups) this has however not been possible.

In summary, the measurable Br^- and Cl^- yields depend strongly on the pH of the solution and, except for Br^- formed in the initial dissociative electron capture process [reaction (10)], result from secondary products.

(2) *Solutions with Other Alcohols.*—The reaction of $^{\bullet}OH$ radicals with primary and secondary alcohols predominantly leads to α-hydroxyalkyl radicals.[21] Such radicals exhibit reducing properties and may therefore be expected to transfer an electron to halothane. Upon radiolysis of nitrogen-saturated solutions containing 0.1 mol dm^{-3} propan-2-ol and 1×10^{-3} mol dm^{-3} halothane at pH 4 both Br^- and Cl^- ions are again the only ionic products formed. The chloride yield of $G(Cl^-)$ 3.0 is of the same order as in the case of t-butyl alcohol-containing solutions (solutions were adjusted to pH *ca.* 10 prior to analysis). The bromide yield of $G(Br^-)$ 60.3 measured under the same conditions is however much higher and exceeds the yield obtained in t-butyl alcohol solutions by one order of magnitude. This high G value indicates a chain reaction with (16) and (10) as initiation reactions, whereas (17) and (18) lead to chain propagation. Every chain cycle [reactions (17) and (18)] yields one bromide ion. Termination of the chain results from bimolecular radical–radical combination according to reaction (13). Other radical–radical reactions, *e.g.* combination of two $(CH_3)_2\dot{C}OH$ radicals or of $(CH_3)_2\dot{C}OH$ with $CF_3\dot{C}HCl$, are impossible at the applied dose rate, since they are not able to compete with reaction (17) (k_{17} 7.6×10^7 mol^{-1} dm^3 s^{-1})[3] at the halothane concentration used.

$$^{\bullet}OH/H^{\bullet} + (CH_3)_2CHOH \longrightarrow H_2O/H_2 + (CH_3)_2\dot{C}OH \quad (16)$$

$$(CH_3)_2\dot{C}OH + CF_3CHBrCl \longrightarrow Br^- + CF_3\dot{C}HCl + H^+ + (CH_3)_2CO \quad (17)$$

$$CF_3\dot{C}HCl + (CH_3)_2CHOH \longrightarrow CF_3CH_2Cl + (CH_3)_2\dot{C}OH \quad (18)$$

The yield of Br^- should depend on the extent of chain propagation which is given by the ratio $k_{18}[ROH][CF_3\dot{C}HCl]/2k_{13}[CF_3\dot{C}HCl]^2$. Hence a change in the bromide yield should occur by varying either the alcohol concentration or the dose rate. Figure 5 shows that the bromide yield does indeed depend linearly on the propan-2-ol concentration as expected, while the chloride yield remains absolutely constant. The linear dependence between $G(Br^-)$ and the propan-2-ol concentration in Figure 5 is quantified[25] by equation (19).

$$G(Br^-) = \frac{k_{18}}{\sqrt{2k_{13}}} \times \sqrt{100N_L G \frac{1}{\text{dose rate}}}[ROH] \quad (19)$$

Introducing $N_L = 6.023 \times 10^{23}$ particles mol^{-1}, dose rate = 300 Gy h^{-1} and $G = 5.7$ (G value of chain start reactions) this equation can be simplified to (19a). From the slope of the

$$G(Br^-) = 2.569 \times 10^4 \times \frac{k_{18}}{\sqrt{2k_{13}}}[ROH] \quad (19a)$$

straight line in Figure 5 $k_{18}/\sqrt{2k_{13}} = 0.0212$ is obtained. Although the rate constant for reaction (13) is not accurately known, an assumed value of the order of 10^9 mol^{-1} dm^3 s^{-1} a seems plausible by comparison with similar reactions reported in the literature.[26,27] Taking $2k_{13} = 1 \times 10^9$ mol^{-1} dm^3 s^{-1} a value of $k_{18} = 670$ mol^{-1} dm^3 s^{-1} is derived for the reaction of propan-2-ol with $CF_3\dot{C}HCl$ radicals {$2k$ referring to $-(d[R]/dt) = 2k[R]^2$}.

Corresponding experiments with other $^{\bullet}OH$ radical scavengers led to the results listed in Table 2. The rate constants for the three reactions (18a) were estimated by the same procedure as described above.

$$\left.\begin{matrix}C_2H_5OH\\CH_3OH\\HCOO^-\end{matrix}\right\} + CF_3\dot{C}HCl \longrightarrow CF_3CH_2Cl + \begin{cases}CH_3\dot{C}HOH\\\dot{C}H_2OH\\\dot{C}O_2^-\end{cases} \quad (18a)$$

The rate constants for hydrogen-atom abstraction by $CF_3\dot{C}HCl$ from the different alcohols decrease in the order $RC(R')HOH > RCH_2OH > CH_3OH$. It is reasonable to assume that this order is governed by the stabilisation energy of the various α-hydroxyalkyl radicals, which result from the $+I$ effect of the alkyl substituents.

The chloride yields are completely independent of the system used and correspond to exactly half the yield of primary chain-starting radicals. A determination of the chloride yield in the formate system was not possible, because formate and chloride elute at almost the same time from the column.

The stable CF_3CH_2Cl formed in reaction (18a) has been identified by g.c.—m.s. Owing to its high yield in the respective chain reactions this was easy to achieve. Absolute yield measurements were however not possible owing to the lack of standard compound.

(3) *Mechanistic Considerations.*—One of the interesting reactions is bromine-atom abstraction from halothane by $^{\bullet}CH_2C(CH_3)_2OH$ radicals with subsequent hydrolysis in basic environment [reactions (11) and (12)]. Similar processes may be expected for other non-reducing radicals in their reaction with compounds containing weakly bound halogens with a polarizable electron cloud. Recent investigations,[28] for example, showed that phenyl radicals $C_6H_5^{\bullet}$ can abstract bromine and iodine atoms from α-substituted carboxylic acids but no chlorine abstraction was observed from the respective analogues.

It is possible that α-hydroxyalkyl radicals also abstract the bromine atom from halothane rather than undergoing an electron-transfer process. However, α-halogenoalcohols which would result from reactions (20) are known to decompose spontaneously in aqueous solution[29] giving the same products as direct electron transfer (21) and thus it would not be possible to distinguish between the two mechanisms.

$$CF_3CHClBr + R\dot{C}(R')OH \longrightarrow CF_3\dot{C}HCl + \underset{\displaystyle Br}{\underset{|}{RC(R')OH}} \quad (20)$$

$$\underset{\displaystyle Br}{\underset{|}{RC(R')OH}} \longrightarrow Br^- + H^+ + RR'CO \quad (21)$$

In one case however the results do possibly provide evidence for an abstraction mechanism. $\dot{C}O_2^-$ radicals had been shown to be unreactive towards CCl_4.[30] No chloride formation was observed in irradiated CCl_4–formate systems, although the polarographic half-wave potential of $\dot{C}O_2^-$ is as negative as that of the $(CH_3)_2\dot{C}OH$ radical,[31] which readily reduces CCl_4.[30] In the present investigation it was now shown that $\dot{C}O_2^-$ does however react with halothane. These findings can easily be explained by an abstraction process considering that the bond energy of C–Br is much lower than that of C–Cl, provided of course that the halogen-atom abstraction is the rate-determining step in the reaction of $\dot{C}O_2^-$.

Another interesting point emerges from comparison of the rate constants measured in this study for $CF_3\dot{C}HCl$, and reported rate constants for respective $\dot{C}Cl_3$ reactions. Thus hydrogen abstraction by $CF_3\dot{C}HCl$ from all alcohols studied is almost ten times as fast as by $\dot{C}Cl_3$, the $\dot{C}Cl_3$ data having been determined by an indirect method,[30] similar to that employed in this study. Although the rate constant for

$$\dot{C}Cl_3 + \dot{C}Cl_3 \longrightarrow C_2Cl_6 \quad (23)$$

may differ slightly from $2k_{13}$ for the dimerization of two $CF_3\dot{C}HCl$ radicals this difference is unlikely to be responsible for the observed differences in the rate constant for hydrogen abstraction. In fact $2k_{13}$ and $2k_{23}$ would have to differ by two orders of magnitude to account for the experimental data. It seems more likely that another parameter plays a more important role, namely the structure of the attacking halogen-containing radical. It was shown by e.s.r. measurements that $CF_3\dot{C}HCl$ is a π-radical with planar sp^2-hybridization.[32] $\dot{C}Cl_3$ on the other hand is generally considered to be pyramidal, with a calculated angle of 101.2° between the C_{2v} symmetry axis and any of the C–Cl bonds.[33] This non-planarity is caused by the three electron-withdrawing chlorine substituents. In the transition state hybridization of $\dot{C}Cl_3$ has to change from sp^2 to sp^3. For energetic reasons this is probably easier to achieve for the $CF_3\dot{C}HCl$ radical than for the $\dot{C}Cl_3$ radical where repulsion of three equal electron clouds has to be overcome. Additionally, the planar $CF_3\dot{C}HCl$ radical can approach the alcohol α-hydrogen atom from both sides while the pyramidality of $\dot{C}Cl_3$ allows attack only from one side. Any inversion at the radical centre would require a small but distinct quantity of energy, which for other non-planar radicals has been shown to be in the range of 4—20 kJ mol^{-1}.[34] In any case, all these structurally and electronically related effects would result in a higher activation energy for the hydrogen abstractions by $\dot{C}Cl_3$ and consequently in lower rate constants for these reactions.

Conclusions.—The one-electron-induced reduction mechanism of halothane qualitatively compares well with that of CCl_4. A significant difference is however a fast reaction of $\dot{C}O_2^-$ radicals with halothane, which does not take place with CCl_4. The results may be viewed as support for a common general mechanism for the reduction of organic halides. Considering that free-radical-induced processes appear to be an informative probe for metabolic processes of halothane[2-4] the present results would also provide further rationale for the formation of products observable in biochemical systems.

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