VALIDATION OF THE SIFT TECHNIQUE FOR TRACE GAS ANALYSIS OF BREATH USING THE SYRINGE INJECTION TECHNIQUE

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(Received 14 November 1996)

Abstract—The selected ion flow tube (SIFT) is a technique originally developed for the determination of rate coefficients for gas phase reactions. Recently the SIFT has been applied to the detection of trace gases in air and breath. The SIFT method is capable of determining absolute partial pressures of trace gases in air without the need for calibration. However, it is necessary to show that SIFT determinations are of acceptable accuracy. This study reports the findings of a validation study in which eight trace gases in air, in the concentration range of 100 ppb–30 ppm, were simultaneously detected and quantified. In addition, the results of the measurement of the partial pressure of perchloroethylene (C₂Cl₄) on the breath of a volunteer some 16 h after a controlled exposure are reported. This study demonstrates that several gases in breath can be rapidly quantified from just a single exhalation. Crown copyright © 1997 Published by Elsevier Science Ltd

INTRODUCTION

The measurement of solvent vapours and their metabolites in expired air is gaining popularity in workplace health risk management programmes (Wilson, 1986; Foo et al., 1991; HSE, 1992; Yasugi et al., 1994; ACGIH, 1995). As a consequence, a number of analytical methods have been developed (Wilson, 1986; Money and Gray, 1989; Phillips and Greenberg, 1992; Peragio et al., 1994). Recently, the selected ion flow tube (SIFT) technique, which was originally developed for the study of ionic reactions in the gas phase (Smith and Adams, 1987), has been applied to the identification and quantification of trace gases and vapours in air and exhaled breath (Španěl et al., 1996; Španěl and Smith, 1996a).

The SIFT analytical method is capable of determining the absolute partial pressure of trace gases without the need for calibration with standard mixtures of gases and vapours. However, it is necessary to validate the accuracy and precision of the technique using an established methodology for generating standard atmospheres of organic vapours. In this paper, we report the results of a validation study in which the standard atmospheres were generated, using the syringe injection technique (HSE, 1990). We also present the results of an experiment in which the

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concentration of perchloroethylene in exhaled breath of a volunteer was determined, 16 h after his controlled exposure to an atmosphere containing a known amount of perchloroethylene.

The principle of the SIFT technique

The principle of the SIFT analytical method is described in detail elsewhere (Smith and Španěl, 1996; Španěl and Smith, 1996b); a schematic diagram of the SIFT is shown in Fig. 1. Basically, a current of primary ions of a given mass-to-charge ratio (for example H$_3$O$^+$, O$_2^+$) is extracted from the ion source via a quadrupole mass filter and injected into the fast flowing carrier gas (such as helium). The organic vapours/gases in air sample introduced into the carrier gas react with the primary ions, resulting in characteristic product ions. For example, acetone (CH$_3$COCH$_3$) will react with H$_3$O$^+$ to produce protonated acetone (CH$_3$COCH$_3$.H$^+$) ions. After the mass separation of the product ions by the downstream mass spectrometer, the primary and product ions are detected and counted by a channeltron/pulse counting system. The resulting mass spectra are then recorded by an on-line computer.

It can be readily shown (Smith and Španěl, 1996) that when the concentration of a trace gas is very small, the primary ion count rate is only slightly reduced by the reaction and the count rates of the product ions are directly proportional to the partial pressure of the trace gas. If the product ions of the reactions of each trace gas are known, the partial pressures of the trace gases in a multi-component mixture can be calculated from the observed count rates of each product ion species.

VALIDATION OF THE SIFT

Standard atmospheres

In this study, we used a mixture of known concentrations of benzene, toluene, m-xylene, acetone, 2-butanone, 1-methoxy-2-propanol and trichloroethylene in ethanol to validate the SIFT. Accurately weighed amounts of each solvent were mixed (diluted) with ethanol in a 25-ml volumetric flask. This stock solution was then used in a motor-driven syringe to inject known amounts into a stream of...
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dry air of known flow rate (HSE, 1990). Using this technique, we prepared partial pressures in the air ranging from about 100 ppb to about 1.5 ppm, which are typically found on the breath of workers who are exposed to these solvents. The concentrations of the ethanol varied over a wide range (1.8–30 ppm). In all, ten dilutions in air were used.

**Sampling**

The air samples were introduced directly into the inlet port of the SIFT (see Fig. 1). A total of eight trace gases, including the ethanol, reacted with the $\text{H}_3\text{O}^+$ ions producing eight major product ions. The count rates of the product ions and the primary ions were obtained by rapidly switching the detection mass spectrometer between the appropriate ion masses. In this study, the product ion count rates varied from a few counts per second (at low concentrations) to several thousand counts per second at the higher concentrations of the abundant ethanol. The count rates of the protonated ethanol molecules were a significant fraction of the $\text{H}_3\text{O}^+$ ion count rate, and this had an undesirable influence on the analytical procedure (see Results and Discussion).

Duplicate measurements were made at each of the 10 dilution levels. To achieve an acceptable accuracy and precision (BS EN 482, 1994), especially at the low concentration levels, SIFT count rate data were obtained for 1 min for each dilution in which time the signal of each product ion was integrated for 5 s. The count rate data were then immediately analysed by the on-line computer using software specifically developed to calculate the partial pressures of each trace gas in the sample. The details of the procedure used for calculating the trace gas concentrations can be found in Španěl and Smith (1996a).

**Perchloroethylene in breath**

A major objective of our research is to use our SIFT analytical method for the rapid, quantitative analyses of trace gases in exhaled breath of workers exposed to substances hazardous to health. In order to illustrate its applicability, breath samples were obtained from a volunteer, who was exposed (in an exposure chamber) to a controlled atmosphere of perchloroethylene ($\text{C}_2\text{Cl}_4$) at a partial pressure of 50 ppm for 2 h. Some 16 h post-exposure, the breath samples were introduced into the SIFT via the heated sampling port. The samples were either collected in a Tedlar bag prior to the introduction to SIFT or introduced directly to the SIFT by displacing the ambient air at the entrance to the sampling inlet with exhaled breath. Direct sampling has two advantages: it avoids the problem of adsorption on to sample bag surfaces (Posner and Woodfin, 1986); and it enables the observation of the real time fluctuations in the flow of trace gases from the respiratory tract.

As $\text{H}_3\text{O}^+$ ions do not efficiently protonate $\text{C}_2\text{Cl}_4$ molecules [the proton affinity of $\text{C}_2\text{Cl}_4$ is less than the proton affinity of $\text{H}_2\text{O}$ (Lias et al., 1988)], $\text{O}_2^+$ ions were used as the primary ion. The reaction then involved is charge transfer, as illustrated in Equation (1).

$$\text{O}_2^+ + \text{C}_2\text{Cl}_4\text{C}_2\text{Cl}_4^+ + \text{O}_2.$$ (1)
RESULTS AND DISCUSSION

In this SIFT technique, the fragmentation of organic molecules into different ionic fragments is much less likely when compared to conventional electron impact ionization mass spectrometry, but mass coincidences of protonated molecules of different organic compounds and their water clusters can occur. There are two examples in these validation data. One was observed at a mass-to-charge ratio of 73 Da (that is at a mass of 73 u since all the ions with which we are concerned are singly charged), resulting from protonated 2-butanone (C_2H_5COH^+CH_3) and the product of the reaction of 1-methoxy-2-propanol with the H_3O^+ ions, as shown in Equation (2).

\[
\text{H}_3\text{O}^+ + \text{CH}_2(\text{CH}_3\text{O})\text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{CH}_2(\text{CH}_3\text{O})\text{CH}_2\text{CH}_2^+ + 2\text{H}_2\text{O}. \quad (2)
\]

This is an H_2O elimination reaction that often occurs when alcohols are protonated by the H_3O^+ ion. When coincidences of this nature occur, the SIFT method of analysis provides the sum of the partial pressures of the two trace gases involved in the mass coincidence. Another overlap occurs at a mass of 93 u between the protonated toluene molecule (C_7H_8^+) and the proton-bound dimer of ethanol (C_2H_5OH.H^+.HOC_2H_5). This overlap did not prevent the determination of toluene concentrations, however.

The majority component ethanol

The results obtained for ethanol are presented in Fig. 2. There is a good correlation (correlation coefficient \(r = 0.998\)) between the syringe injection method and SIFT determinations. However, it is clear that the SIFT measurements are somewhat higher (slope of the regression = 1.12). The highest concentration point is

![Fig. 2. A plot of the ethanol partial pressure measured using the SIFT technique (ordinate) as a function of the ethanol partial pressure in a test atmosphere generated by the syringe injection technique (abscissa). The solid line with the slope indicated represents the least-squares fit through all the data points with the exception of the highest partial pressure point. The dotted line represents the ideal one-to-one correlation. The error bars indicate the expected absolute errors (see the text).](https://academic.oup.com/annweh/article-abstract/41/3/373/172224/41/3/373/172224)
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obviously above the line. This is due to the fact that the count rate of the protonated ethanol ion is then a significant fraction of the primary ion (H$_3$O$^+$) count rate (see previously). A correction for this non-linearity can be made using a more sophisticated analysis, which takes into account the reduction of the primary ions along the flow tube (Španěl and Smith, 1996b). In practice, however, the complications arising from excessively high partial pressures of trace gases may be mitigated by lowering the sampling flow rate.

The 12% discrepancy is mainly due to the combined systematic error (and not due to random errors) inherent to the SIFT and syringe injection techniques. The factors that significantly contribute to the systematic errors in the SIFT measurements are: the carrier gas and sample gas flow rates; the ion count rate ratio due to the trace gas ions and the precursor ions; and the rate coefficients for the proton transfer reactions. From a detailed consideration of the potential errors arising from these sources, we estimate an overall error of ±17%. The overall error for the standard generation system is in the region of ±15%. Hence, the observed 12% discrepancy is easily accounted for.

**Benzene and acetone**

The correlation coefficients and the slopes of the calibration plots for these two different organic molecules, a non-polar aromatic hydrocarbon and a very polar aliphatic ketone, were found to be very close (slopes = 1.12; $r = 0.993$, $r = 0.997$). The slopes of the plots (Fig. 3) again indicate systematic differences between the SIFT and the syringe method. Again, the errors encountered are well within the acceptable limits. Note that the regression lines given in Fig. 3 extrapolate through the origin of coordinates.

![Fig. 3. Plots of the measured partial pressures of benzene (a) and acetone (b) versus the generated partial pressures (following Fig. 2). The data were obtained simultaneously with the data for ethanol shown in Fig. 2.](https://academic.oup.com/annweh/article-abstract/41/3/373/172224/41373172224)
Xylene and trichloroethylene

Once again, very high correlations ($r = 0.990$ and $0.994$, respectively) are seen. The slopes for these plots were 1.02 and 1.06, respectively (see Fig. 4), which are somewhat lower than those obtained for ethanol, acetone and benzene. The reason for the somewhat lower slopes in these cases may be due to a slight mass discrimination in the detection quadrupole mass spectrometer at these higher ionic masses, and because of the 'sticky' nature of these vapours. (Note the departure from linearity of the curve for xylene and trichloroethylene at the lowest partial pressures.)

2-Butanone and 1-methoxy-2-propanol

Because of mass coincidence (as explained earlier), it was not possible to determine the concentrations of these compounds individually. In these circumstances, it would be necessary to use an alternative precursor (for example, $O_2^+$) to avoid mass coincidences. When the sum of the partial pressures, determined by the SIFT, was compared to the sum of partial pressures expected from the syringe method, we found a very good correlation (slope 1.06; $r = 0.991$; see Fig. 4). This experiment showed that issues relating to the mass coincidences should be taken into careful consideration when unknown samples are analysed.

Toluene

We observed mass coincidence at 93 u because of the protonated toluene ion and the proton-bound dimer of ethanol. The effect of this mass coincidence is shown in Fig. 5 (curved line). The non-linearity is due to a relatively high concentration of ethanol resulting in a three-body reaction to produce a proton-bound dimer of ethanol. When this three-body reaction is accounted for in the kinetic analysis, the resulting plot for toluene is acceptable ($r = 0.992$). The problems seen with these SIFT determinations of toluene, 2-butanone and 1-methoxy-2-propanol demonstrated the need for an excellent knowledge of the ion chemistry. This issue is of great importance when SIFT is used for direct trace gas analysis of complex mixtures.

Perchloroethylene in breath

The mass spectrum of the ions formed by the ionization of the molecules in the breath samples collected in a Tedlar bag is shown in Fig. 6(a). An obvious feature of this mass spectrum is the several ions at the high mass resulting from the presence of $\text{C}_2\text{Cl}_4$. For the $\text{C}_2\text{Cl}_4^+$ ions formed by the charge transfer reaction [see Equation (1)], there are five isotopic variants at masses 164 (31.9%), 166 (42.2%), 168 (20.6%), 170 (5.0%) and 172 (0.4%) [see Fig. 6(b)].

The count rates for these isotopic variants were included in the determination of the partial pressure of $\text{C}_2\text{Cl}_4$ in the breath sample, which was found to be 1070 ppb. This concentration is close to the anticipated concentration of $\text{C}_2\text{Cl}_4$ in breath 16 h after exposure to 50 ppm for 2 h (Hake and Stewart, 1977). The mass spectrum in Fig. 6(a) shows the presence of the common breath trace gases acetone, ethanol and isoprene (Manolis, 1983).
Fig. 4. Plots of the measured partial pressures of xylene (a) and trichloroethylene (b) versus the generated partial pressures (following Figs 2 and 3). These two solvents are more surface-active than ethanol, benzene or acetone (see Figs 2 and 3), and this results in a more obvious scatter of the data points about the fitted lines and a noticeable increase above the expected partial pressures at very small generated partial pressures. The sum of the partial pressures of 2-butanone and 1-methoxy-2-propanol is plotted in (c) because of the overlap of the molecular masses of the corresponding product ions.
Fig. 5. A plot of the measured partial pressures of toluene (a) versus the generated partial pressures (following Fig. 2). The data were obtained simultaneously with the data shown in Figs 1-3. The open squares indicated the values calculated from the total count rate of the ions at 93 u. The obvious curvature of the dotted line through the data points is due to the production of the ethanol proton bound dimer. The filled squares represent the data points for toluene alone obtained by correcting for the dimer ion formation (see text).

The data obtained when the breath sample were directly introduced into the SIFT is shown in Fig. 6(c). The fluctuations in measured partial pressures with time, during the single breath exhalations, are the real variations of the C$_2$Cl$_4$ flow from the respiratory tract. From these data, the mean concentration of C$_2$Cl$_4$ in breath was found to be 1180±70 ppb, which is somewhat higher than the bag sample result given above and was expected. Our normal approach to breath sampling is first to use a bag sample to identify the trace gases present and then to use the direct sampling method for quantitative analysis.

CONCLUSIONS

By this validation study, we have shown that the SIFT technique can be used for the rapid, accurate quantitative analysis of many trace gases in air and breath, in the partial pressure range from 100 ppb to 30 ppm, without the need for prior calibration using standard atmospheres. However, the partial pressure ranges reported in this paper are not the limit for the instrument, because the upper and lower limits ranges can be extended by altering the critical parameters, such as the sample flow rate and the ion integration time. A valuable feature of the method is that partial pressures of specific trace gases on breath can be determined from a single exhalation in real time.

Mass coincidences, resulting from ionic species from different molecules, were observed. This issue may present some difficulties when complex mixtures are to be analysed, but these occasional difficulties can be overcome by a good understanding of ion chemistry involved. An extensive library of rate coefficients and the ion products of ion–molecule reactions is required. This library would provide
Fig. 6. (a) A SIFT mass spectrum of a bag sample of the breath of a volunteer 16 h after controlled exposure for 2 h to a standard atmosphere containing 50 ppm of perchloroethylene. The precursor ions (open bars) and the product ions corresponding to the common breath trace gases and perchloroethylene (filled bars) are as indicated. (b) A detailed mass spectrum of the isotopic variant ions of C_2Cl_4 indicating the observed percentages of each isotopic variant. The corresponding percentages calculated on the basis of the natural isotopic abundances are essentially identical as 31.9% (164 u), 42.2% (166 u), 20.6% (168 u), 5.0% (170 u) and 0.4% (172 u). (c) The time profiles of the perchloroethylene partial pressure recorded on the breath of the volunteer during four independent exhalations with their average values across the peak of the exhalation profile in ppb as indicated. The precursor ions are O_2. These profiles were obtained by rapidly switching the SIFT mass spectrometer between the primary ion and C_2Cl_4 product ions (see the text).
information on primary ions to be used and the molecules to be detected. The conventional SIFT studies of appropriate ion–molecule reactions are taking place to help towards the goal of building a library.

Acknowledgements—We thank Peter Rolfe and John Thompson for many stimulating discussions, and the HSE Ethics Committee for approving the volunteer study.

REFERENCES


