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A general method for the calculation of absolute trace gas concentrations in air and breath from selected ion flow tube mass spectrometry data

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We dedicate this paper to the memory of Professor Chava Lifshitz, an early researcher into selected ion flow tube techniques, in recognition of her outstanding pioneering work and major contributions to gas phase ion chemistry.

Abstract

A complete description is presented of a numerical method that allows the calculation, in real time, of absolute concentrations of trace gases, including volatile organic compounds and water vapour, from selected ion flow tube mass spectrometry, SIFT-MS, data. No assumptions are made concerning the SIFT-MS instrument size or its configuration and thus the calculation can be applied to the currently available, relatively large instruments and the anticipated new generation of smaller SIFT-MS instruments. This numerical method clearly distinguishes those parameters that are obviously specific to a particular instrument, including flow tube geometry, degree of mass discrimination in the analytical mass spectrometer and flow tube reaction time, from general fundamental processes, in particular the differential diffusive loss of ions along the flow tube that is dependent on the properties of those ions involved in the determination of the concentrations of particular trace gases. The essential reaction and transport kinetics are outlined, which describe the formation and loss of the product ions formed in the chemical ionisation of the trace gases by the precursor ions. A generalised calculation of the required ionic diffusion coefficients is introduced with options either for their accurate determination from the molecular geometry of ions or for less accurate but simpler estimates obtained using just the ionic mass. Based on the above ideas, a straightforward calculation sequence is shown to determine trace gas concentrations by SIFT-MS, and its utility demonstrated by an example of the analysis of acetone in exhaled breath.

Keywords: Selected ion flow tube; Mass spectrometry; SIFT-MS; Trace gas analysis; Breath analysis; Volatile organic compounds

1. Introduction

Accurate quantitative analyses of trace gases in air often need to be achieved in real time with short time resolution (seconds), especially when on-line analysis is desired, avoiding the use of stored samples, as is the case for exhaled breath analysis for clinical diagnosis and therapeutic monitoring [1,2]. Few analytical methods can achieve this, especially when it is required to simultaneously identify and quantify several trace gases that may range in complexity from diatomic molecules such as nitric oxide and carbon monoxide, small polyatomic molecules like nitrogen dioxide, ammonia and ethane and complex organic molecules such as alcohols, ketones and hydrocarbons, many of which often occur in polluted air and exhaled breath. Stimulated by our interest in breath analysis in physiology and medicine, and hence to perform real time, on-line analyses of breath, we have developed the selected ion flow tube mass spectrometry, SIFT-MS, analytical method [2,3]. Using SIFT-MS, on-line analyses of single exhalations of breath for several metabolites can be achieved simultaneously down to the ppb level [2]. Thus, breath analysis for the major metabolites is rapid, painless and accurate, and temporal variations can be studied on time scales of seconds [4]. The various pilot investigations demonstrating the potential value of SIFT-MS in medicine are reported in a recent review article [2] and in a recent book, which also describes other analytical methods used for breath analysis [1].

Of course, meaningful gas analysis involves both proper identification of the composite trace gases in the air/breath mixture

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and their accurate quantification. A major objective is to obviate constant calibration of the analytical instrument for the many trace gas compounds that may be present. This is fulfilled by SIFT-MS, as long as the ion chemistry and the physics of the ion transport processes that underpin this analytical method are properly understood. These crucial aspects have been continuously researched and become increasingly understood since the inception of SIFT-MS; progress has been reported in numerous research publications and summarised in the recent *Mass Spectrometry Review* article [2]. Our recent work on the diffusion of complex ions in rare gases [5], and in particular the computation and measurement of diffusion coefficients, have finally closed the complex loop that now allows accurate quantification of a wide variety of trace gases in ambient air and the very humid air that is exhaled breath.

It is the objective of this paper to quantitatively describe the detailed physical processes, including differential diffusion, that are involved in SIFT-MS analyses and clearly plot the steps involved in the absolute quantification of trace gases in complex mixtures such as exhaled breath. It should serve also as an essential guide for new users of the SIFT-MS technique for quantitative analysis and as the basis and reference for the analytical software.

2. Brief overview of the basic principles involved in SIFT-MS

SIFT-MS involves chemical ionisation, using selected precursor positive ions, of the trace gases in an air/breath sample that is introduced into a flowing gas in a flow tube. The detailed principles involved in this analytical technique and its exploitation for breath analysis in medicine and other areas are given in several papers [2,3,6]. A line diagram of the SIFT-MS instrument is shown in Fig. 1. In brief, H_3O^+, NO^+ or $O_2{}^+$ precursor ions are injected into fast flowing helium carrier gas in the flow tube. Then the gas to be analysed, e.g., exhaled breath, displaces the ambient air at the entrance to an open port and thus a sample of the gas enters the carrier gas/ion swarm via a calibrated capillary. The capillary and the connecting tubes are all heated to about 100 °C to prevent condensation of water and other condensable species. The reactions of the precursor ions with trace gases in the air/breath lead to the characteristic product ions that identify the trace gas compounds; their count rates are used in the quantification of the trace gas. The ion chemistry involved in SIFT-MS has been reported in several papers (for example [7–10]) and reviewed in [2].

The precursor ions and the product ions in the carrier gas are sampled into a downstream quadrupole mass spectrometer, a channel electron multiplier being used for pulse counting of the mass selected ions. This mass spectrometer can be scanned over chosen ranges of mass-to-charge ratio, *m*/*z*, for a given time period, thus producing mass spectra. This is called the mass scan or full scan mode of operation. The resulting mass spectra, allied to an appreciation of the ion chemistry occurring, are used to identify the neutral species present in the air/breath sample. In the multi-ion monitoring (MM) mode of operation, ion intensities are recorded at several specific *m*/*z* values by rapidly switching the mass spectrometer to target the precursor ions and some chosen product ions. By this means, rapid changes in the trace gas concentrations can be tracked, for example, through single breath exhalations [2,4,11]. It is the objective of the following sections to fully document the numerical data processing required to calculate the concentrations of the trace gases in an air or breath sample from the ion count rates recorded by the

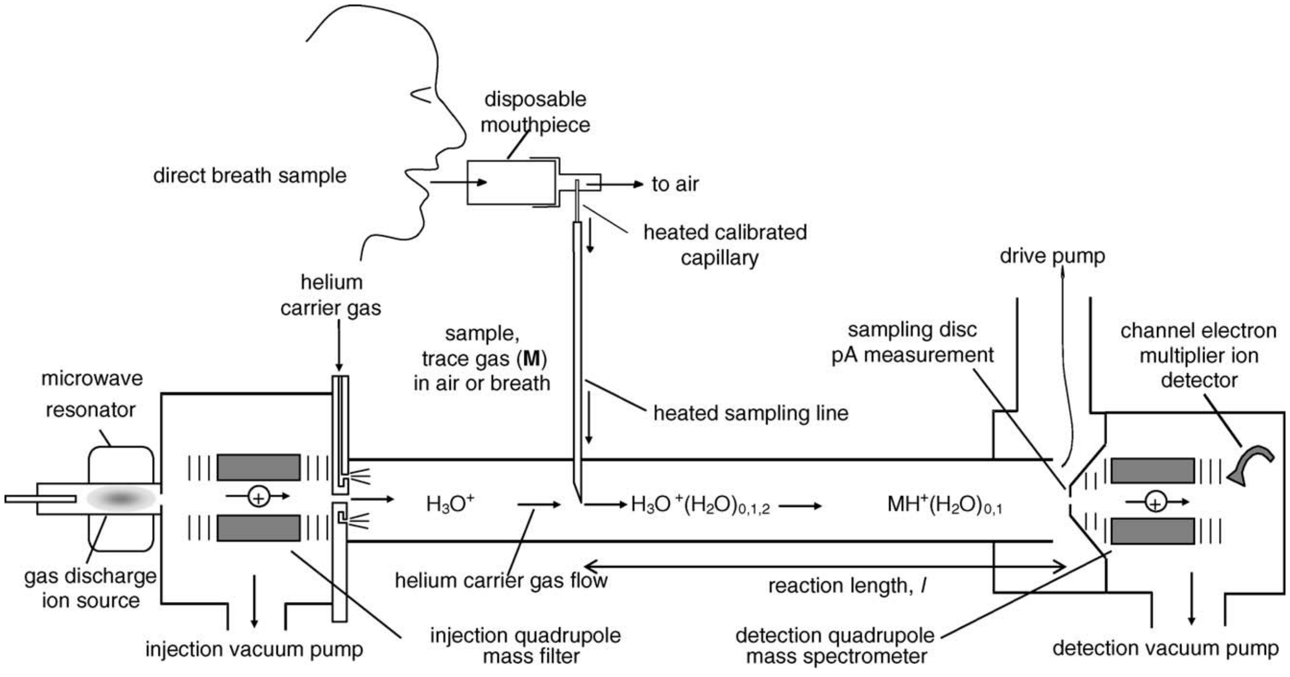

Fig. 1. Schematic diagram of the SIFT-MS instrument showing the essential parts. It is configured for the analysis of trace gases in exhaled breath. The elements of the ion chemistry occurring between the H_3O^+ precursor ions and the breath metabolites, M, are as indicated.

analytical mass spectrometer using the physical quantities of flow rates, pressures, temperature, the known rate coefficients of the precursor ion/trace gas molecule reactions and the diffusion coefficients of all the ions involved (see Section 3.3 below).

3. The numerical method for calculating absolute trace gas concentrations

This section traces step-by-step the numerical analysis of SIFT-MS data to obtain absolute concentrations of trace gases in air and breath samples. All the equations presented are used in the calculation, and the sequence in which they are given follows the flow of the calculation from the raw experimental data to the required trace gas concentration. The essential physics underlying the calculation is also indicated, but the use of equations that are not required for the final numerical data analysis is avoided.

3.1. Processing of the instrumental data

Before discussing the procedures that are closely related to the general features of the SIFT-MS method, it is useful to briefly review some necessary processing of the acquired data that will be specific to and possibly different for different SIFT-MS instruments. The physical quantities that have to be measured are listed here:

(i) *Flow rate of the sample—air or breath*. The most common arrangement for SIFT-MS analyses involves the use of a heated, calibrated sampling capillary, as depicted in Fig. 1. This limits the surface area of tubing exposed to the air/breath sample and minimises the loss of condensable trace gases by surface adsorption. Hence, memory effects are essentially eliminated, which ensures that the response time of the instrument remains short enough to allow the time profiles of breath metabolites to be observed (as will be shown later in Section 4). The calibration of the capillary is performed using an in-line flow meter, which is used to measure the flow rate of air that is needed to produce the same pressure increase in the flow tube that occurs when the sampled air is introduced through the capillary. The flow meter is normally excluded when analysing samples. It is important to note that the capillary temperature influences the air viscosity and so this temperature should be stabilised and monitored during these calibration measurements and during all analyses.

(ii) *Flow rate of the helium carrier gas*. This is a straightforward measurement, usually achieved using a mass flow controller with the manufacturers' calibration and an appropriate gas correction factor for helium. Most flow controllers require regular zeroing.

(iii) *Flow tube pressure*. All SIFT-MS instruments must have a gauge to determine and monitor the flow tube pressure. The numerical data processing varies with the type of gauge used and involves the application of gas-specific calibration curves for Pirani-type gauges and periodic zeroing of capacitance manometers. A calibration factor may be applied to account for any pressure drop between the position of the gauge coupling to the flow tube and the desired carrier gas pressure at the mid-point along the reaction zone of the flow tube.

(iv) *Flow tube temperature*. The flow tube temperature is another key parameter for quantitative SIFT-MS analysis. It is measured by a calibrated sensor placed on the flow tube. A periodic check of the sensor calibration at room temperature before commencing measurements should be part of good SIFT-MS practice. An inaccurate flow tube temperature can seriously compromise the accuracy of trace gas quantification (see Eq. (17) later).

(v) *Precursor and product ion intensities*. The analytical mass spectrometer data (i.e., the precursor and product ion count rates) are obtained as count rates of pulses generated by a channel electron multiplier. Such data reflect the composition of the ion swarm arriving at the downstream sampling orifice (see Fig. 1). The physical quantities required are the relative number densities of ions of different mass-to-charge ratio, m/z. However, there are two important effects that must be accounted for to obtain this information: one is the effective dead time of the electron multiplier/pulse amplifier/discriminator combination, τ_d, which, if not accounted for, can distort the count rates if they are too high, and the other is any mass discrimination in the analytical spectrometer/ion detection system. The latter results from the combined effect of the varying transmission efficiency of the analytical quadrupole with m/z when it is operated at the required unit resolution for all m/z values, and the decreasing sensitivity of the channel electron multiplier with increasing m/z. The τ_d can, in practice, be characterised using the known abundance ratio between two isotopomers (which usually vary in intensity by two-to-three orders-of-magnitude, e.g., the $^{18}O/^{16}O$ ratio in the O_2^+ molecular ions in the swarm is 4×10^{-3}). The mass discrimination factor for each m/z value, M_r, can be characterised by relating the measured ion count rates to the ion current collected by the downstream sampling disc (see Fig. 1), as measured by a built-in picoampere meter, as ions of a single specie at known m/z value are created in the helium carrier gas [6]. For quality control, good practice involves the routine recording of this disc current and ideally its variation during the analysis caused by a change in the ion swarm composition.

The procedure currently adopted in the present SIFT-MS instruments to correct the count rate data for these two effects can be described by the following sequence of calculations. M_r for a given m/z value is obtained using the empirical formula:

$$M_r(m/z) = 1 + f_{m1}(m/z - 19) + f_{m2}(m/z - 19)^2 \qquad (1)$$

The integer 19 appears here as the reference m/z value of the commonly used H_3O^+ precursor ion in SIFT-MS analyses. The values of the constants f_{m1}, f_{m2} have to be determined experimentally [6] for a given resolution setting of the analytical quadrupole mass spectrometer, as described above. However, Eq. (1) should be used with caution, as it is entirely empirical for a given type of a quadrupole mass spectrometer and there is no fundamental reason why it should be applicable to other types of quadrupole. The dead time corrected ion signal, I, can be calculated from the multiplier count rate (number of accumulated counts, N, divided by the acquisition time of the counts, t_s) as:

$$I = M_r(m/z)\frac{N/t_s}{1-\tau_d N/t_s} \tag{2}$$

Important supplementary information that can be obtained at this stage is the relative standard error, R.E., of the ion signal measurement taken as the estimated Poisson variance (counting statistics) [12] as:

$$\text{R.E.} = \frac{\sqrt{N}}{N} \tag{3}$$

In the subsequent discussion it will be assumed that the correction of the mass spectrometer data for mass discrimination and multiplier dead time have been carried out and that after this processing the ion signals, I, for each ion specie are proportional to their individual concentrations just outside the downstream ion sampling orifice.

All the quantities mentioned in this Section 3.1 represent the raw data that should be routinely stored for a SIFT-MS analysis, so that later re-analysis and auditing is possible, ensuring that the quantification is traceable back to all the individual parameters involved.

3.2. Reaction time

The injected ions are convected along the flow tube by the carrier gas moving with a laminar flow pattern and the air sample is introduced into the flow tube by an inlet port at a fixed location, as shown in Fig. 1. As the speed of the carrier gas flow is constant, the reaction time, t_r, during which the precursor ions react with the trace gas molecules in the air sample, is well defined and, in practice, is constant for any given SIFT-MS instrument at a given carrier gas pressure. Thus, t_r can be obtained from the ion flow velocity, v_i, which is related to the gas flow speed, v_g, and the length of the reaction region, l. There are two possible ways to obtain the flow speed of the carrier gas, v_g:

(i) *Calculation of* v_g *from the measured gas flow rates*. This method has been traditionally used in the large static laboratory instruments and also in the first generation of the transportable SIFT-MS instruments engineered by Europa Scientific Limited, UK (instruments which forthwith will be designated Mk.l and Mk.2). A mean gas bulk velocity, v_g, is first calculated from the total gas flow rate, including the carrier gas flow rate, Φ_c, and the sample air flow rate, Φ_a, the measured flow tube pressure, p_g (Torr), and the flow tube gas temperature, T_g, and the geometrical internal cross section of the flow tube, A, thus:

$$v_g = \frac{\Phi_c + \Phi_a}{p_g}\frac{1}{A}\frac{T_g}{T_{20}} \tag{4}$$

Here, $T_{20} = 293.15$ K is the normal temperature used in the calibration of the flow meters (in units of Torr l s^{-1}) that provide the value of Φ_c. The specific feature of this method is that the reaction time is automatically re-calculated for every individual measurement of trace gas concentration.

(ii) *Calculation of* v_g *from the pumping speed of the drive pump*. In order to simplify and to produce the new generation of smaller SIFT-MS instruments, it is often desirable to avoid the need for carrier gas and/or sample gas flow controllers or flow meters. In such situation the reaction time can be calculated from the known pumping speed, S, of the drive pump used to establish the carrier gas flow (see Fig. 1). The conductance of the pumping lines at the operating pressure has to be taken into the account to determine the effective pumping speed at the exit of the flow tube. The mean gas bulk velocity, v_g; is then:

$$v_g = \frac{S}{A}\frac{T_g}{T_{20}} \tag{5}$$

As the pumping speed of a particular type of drive pump at a given pressure is dependent only on the frequency of its AC power supply, it can be determined during the factory setup and then assumed to remain constant for a given instrument, as long as the flow tube pressure is reproducible between the measurements (although, obviously, regular checks represent good practice).

Now v_i can be calculated from v_g. The radial ion concentration distribution in the flow tube is established by diffusion to and loss of ions at the wall surface. Thus, the mean velocity of the ions along the flow tube, v_i, which determines the reaction time, t_r, of the ions with a reactant gas, is greater than v_g by a constant factor:

$$v_i = R_v v_g \tag{6}$$

The well established value for R_v for large field-free flow tubes is 1.5 [13]. However, it has to be kept in mind that this is not a fundamental constant for all flow tubes and that it may have somewhat higher values (1.6–1.7) for short flow tubes where the final diffusion distribution takes an appreciable fraction of the reaction length to be established.

Now the reaction time, t_r, is simply calculated from the reaction length, l, obtained from the geometrical distance between the sample inlet port and the sampling orifice (empirically corrected by a so called "end correction" [13] for the finite mixing distance of the sample into the carrier gas) and v_i as:

$$t_r = \frac{l}{v_i} \tag{7}$$

The important point to make here is that even though the commentary to Eqs. (6) and (7) implies some approximations and an empirical correction, these equations are only used to determine the reaction time from measured parameters. However, in the terms of reproducibility and robustness of the SIFT-MS analysis, these factors are all systematic and once an accurate value of reaction time is determined for a given SIFT-MS instrument, it is not subject to any random variations or to variations related to the nature of the trace gas being analysed [12]. The reaction time t_r (without end correction) can also be determined experimentally by applying a positive electrical pulse at the inlet point of the samples and by simultaneously recording the arrival of the disturbance of the ion swarm on the ion detector [13]. This method does not rely on the estimate of R_v, which is instrument-dependent for short flow tubes.

3.3. Kinetics of formation and loss of ionic species in the carrier gas

There are two processes influencing the concentrations of the precursor and product ions in the flow tube. These are ion–molecule reactions, representing loss of reactant (precursor) ions and simultaneous formation of the product ions, and diffusive loss of all of the ions to the flow tube walls. The kinetics of these processes are determined by the chemical and physical properties of the ions and the gases being analysed, i.e., the *rate coefficients*, *k*, for the reactions of all the precursor ions (including the hydrated ions) with the analyte molecules, M, and the *diffusion coefficients*, *D*, for all the precursor ions and the specific product ions, including the hydrates of all the species. This information must be collected before the absolute concentration of any trace gas compound can be calculated. Most end users of SIFT-MS do not need be concerned about this, as the information for a particular application, such as breath analysis for common metabolites [1] or of, for example, biomarkers of tumours [14], is provided within a SIFT-MS kinetics library, supplied by the manufacturer of the instrument. However, researchers who identify a need to quantify compounds not yet included in the kinetics library may find the following subsections useful.

3.3.1. Rate coefficients, k

The required rate coefficients are best obtained from original papers (for example [7–10] or references given in [2]) or from extensive compilations [15,16]. If the required *k* value is not available, it can be measured using the SIFT method in the way that has been well described in the literature [13]. When it is considered that the rate of a reaction will be collisional, as, for example, proton transfer reactions that are exothermic by more than some 25 kJ/mol [17], then the *k* value can be calculated from the polarisability and dipole moment of the neutral molecules using the Su and Chesnavich parameterization [18].

3.3.2. Diffusion coefficients, D

The diffusion coefficients for some ions can be obtained from the literature, mostly as calculated from tabulated reduced mobility values using the Einstein relation [19]. If the required *D* values are not known, they can be calculated accurately from the ionic geometry using the hard-sphere cross section. The detailed theory describing this approach has been published recently [5], so here we just reproduce the essential steps and equations involved in the calculation of *D* values.

Firstly, the molecular geometry has to be obtained for every product ion as a set of *XYZ* coordinates using any standard quantum chemistry package (semi-empirical methods like PM3 [20] are most useful for this purpose). Then, from these geometries, the hard sphere cross section σ_{hs} (in units of $\mathrm{\AA}^2$) for the collisions of a given ion with helium atoms can be calculated using the freely available software by Dryahina [21]. Finally, the value of the diffusion coefficient, *D*, can be calculated using the following straightforward formulae:

$$\bar{\Omega}^{(1.1)} = 0.975\sigma_{\mathrm{hs}} + \left(\frac{40.65}{\sigma_{\mathrm{hs}}}\right)^2 \qquad (8)$$

$$m_{\mathrm{r}} = \frac{m m_{\mathrm{He}}}{m + m_{\mathrm{He}}} \qquad (9)$$

$$D_{1\mathrm{He}} = D_{1\mathrm{He}}(\mathrm{H_3O^+})\sqrt{\frac{3.3}{m_r}\,\frac{\bar{\Omega}^{(1.1)}(\mathrm{H_3O^+})}{\bar{\Omega}^{(1.1)}}} \qquad (10)$$

Here, $\bar{\Omega}^{(1.1)}$ is the collision integral, *m* the ionic mass, m_{He}, the mass of the helium atom, and m_{r} is the so-called reduced mass of the diffusing ion. Eq. (10) is formulated to provide a result relatively to the $\mathrm{H_3O^+}$ ion and thus it uses the reference values for this ion: $D_{1\mathrm{He}}(\mathrm{H_3O^+}) = 421\ \mathrm{cm^2\,s^{-1}}$ at a helium pressure of 1 Torr. The 3.3 figure is the reduced mass for $\mathrm{H_3O^+}$ colliding with He, and $\bar{\Omega}^{(1.1)}(\mathrm{H_3O^+}) = 30.3\ \mathrm{\AA}^2$ is the value of the collision integral for $\mathrm{H_3O^+}$ on He at 300 K.

If only a quick estimate and not an especially accurate value of *D* is required, the approximate correlation between *D* and ion mass-to-charge ratio, *m*/*z*, shown in Fig. 2 as the least squares fit of the results from [5] in the range of *m*/*z* from 10 to 170, can be used:

$$D_{1\mathrm{He}} = 140\ \mathrm{cm^2\,s^{-1}}\ \ln\frac{383}{m/z} \qquad (11)$$

The maximum error incurred in this estimate of the diffusion coefficient in helium at 1 Torr, $D_{1\mathrm{He}}$, should be less then ±50% of the accurate *D* value and typically it will be better than ±20% for protonated organic compounds and their hydrates. Eq. (11) can also be used to provide a default value by the SIFT-MS analytical software in case the accurate diffusion coefficient is not included in the kinetics library.

3.3.3. Kinetics library

The *k* and *D* quantities thus obtained, which are required for the analysis of a particular compound, are compiled into a *kinetics library* and can be used universally on all SIFT-MS instruments of different sizes and types. A sample section of such a kinetics library is shown in Table 1.

Note that the *k* values could be both temperature and carrier/buffer gas (helium) pressure dependent and that the *D* values are always inversely proportional to carrier gas pressure and are also temperature dependent [5]. Thus, the kinetics library contains the values of diffusion coefficient, $D_{1\mathrm{He}}$, for the diffusion of the ions in helium at a nominal pressure $p_1 = 1$ Torr, values which must be adjusted for lower or higher pressures. Argon can be added into the carrier gas to diminish the diffusive loss of ions to the flow tube walls, thus enhancing the number densities of all the ions in the carrier gas and hence the detected signals of both the precursor ions and the product ions downstream. Also, the flow rate of the air/breath sample to be analysed is sometimes a substantial fraction of the helium flow rate. In such situations

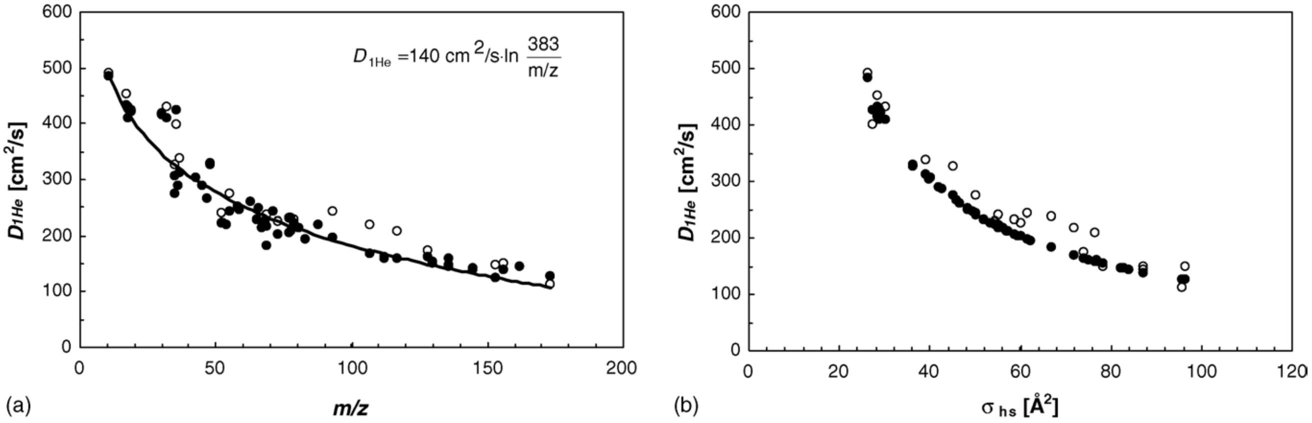

Fig. 2. Values of the diffusion coefficients, $D_{1\mathrm{He}}$, for various ions in helium at a pressure of 1 Torr and a temperature of 300 K. The black points are calculated from the ion geometries [5]; the open points are derived from the published experimental values of ion mobilities (also given in [5]). (a) The correlation of $D_{1\mathrm{He}}$ with the ionic mass-to-charge ratio, *m*/*z*, and (b) The much better but less convenient correlation of D_0 with the geometrical cross section for collisions with helium atoms, σ_{hs} [5].

the effective diffusion coefficients of the ions in the helium/air gas mixture are lower than in pure helium, but they can be calculated by considering the partial pressures of the helium, p_{He}, argon, p_{Ar} and air, p_{Air}; in the flow tube using Blanc's law [19]:

$$D = \frac{p_1}{(p_{\mathrm{He}}/D_{1\mathrm{He}} + p_{\mathrm{Ar}}/D_{1\mathrm{Ar}} + p_{\mathrm{Air}}/D_{1\mathrm{Air}})} \tag{12}$$

When the partial pressures of argon and air are small, it is usually sufficient to approximate the diffusion coefficients for most ions in these heavier gases as seven times smaller than they are in helium [19].

3.3.4. *Differential diffusion enhancement calculation*

Now these fundamental kinetic coefficients can be used to calculate the unknown concentration of analytes in a sample of air or breath. The combined kinetics of the reaction and diffusion processes involved in a SIFT-MS analysis is described by a set of ordinary differential equations [22]. The analytical solution is quite complex even for the simplest case of one precursor ion, H_3O^+, reacting with a single molecular specie, M, that results in a single product ion specie, MH^+. For the purposes of numerical analysis of SIFT-MS data, it is not necessary to repeat the full mathematical analysis here (more details can be found in [2,6,22]). It is sufficient to note that the *differential diffusion enhancement factor*, D_{e} defined as the ratio of the concentrations at the end of the flow tube of the product ions $[MH^+]$ and the change of the concentration of the reacting precursor ions $[H_3O^+]$ due to their reaction with M (see [6] for detailed explanation), can be calculated from the difference between the diffusion coefficients of the precursor and product ions as:

$$D_{\mathrm{e}} = \frac{\exp\left(\frac{D(\mathrm{H_3O^+}) - D(\mathrm{MH^+})}{\Lambda^2} t_{\mathrm{r}}\right) - 1}{\frac{D(\mathrm{H_3O^+}) - D(\mathrm{MH^+})}{\Lambda^2} t_{\mathrm{r}}} \tag{13}$$

Here Λ^2 is the square of the characteristic diffusion length of the vessel, which for a long cylindrical flow tube is calculated from the flow tube cross section, *A*, as $\Lambda^2 = A/18.17$ [19]. Graphical representations of Eq. (13) are shown in Fig. 3 for four different SIFT-MS instruments (different t_{r} and *A*) at their typical working pressures. The "old SIFT" is the first large laboratory instrument used for trace gas analysis [3,14] with a large size Roots pump as the drive pump. The Mk.1 and Mk.2 instruments are two different versions of a smaller transportable TSIFT instru-

Table 1
Sample section of the kinetics library in SIFT-MS for acetone analysis

Compound name	Precursor symbol	Precursor ions			Product ions	
		m/z	*k*	$D_{1\mathrm{He}}$	*m/z*	$D_{1\mathrm{He}}$
Acetone	H_3O^+	19	3.9e−9	421	59	243
		37	3.3e−9	307	77	203
		55	2.5e−9	239		
		73	2.4e−9	202		
Acetone	NO^+	30	1.8e−9	416	88	218
		48	2.5e−9	326		
		66	2.4e−9	246		
Acetone	O_2^+	32	3.1e−9	409	43	301
					58	248

The rate coefficients, *k*, are in units of $\mathrm{cm^3\,s^{-1}}$; the diffusion coefficients, $D_{1\mathrm{He}}$, are in units of $\mathrm{cm^2\,s^{-1}}$. These data relate to a helium carrier gas temperature of 300 K and a pressure of 1 Torr.

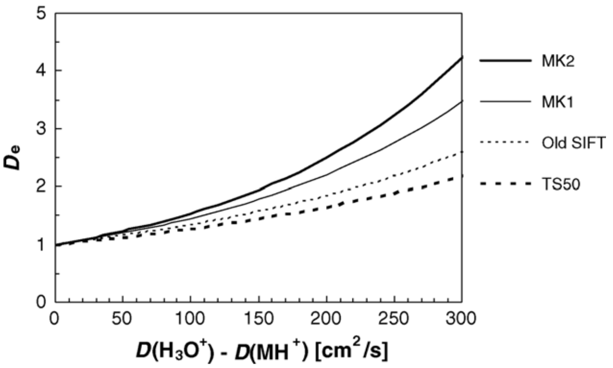

Fig. 3. Values of the differential diffusion enhancement factors D_e calculated from the ionic diffusion coefficients at 1 Torr of He for four different types of SIFT-MS instruments, as described in the text.

ment [6], and the TS50 instrument is the prototype of the next generation, much smaller SIFT-MS instruments (Trans Spectra Limited, UK and Instrument Science limited, UK; private communication). Note that for a difference in the diffusion coefficients between that for precursor H_3O^+ ions and the product ions of about 200 $\mathrm{cm^2\,s^{-1}}$, the highest value $D_e = 2.5$ is for the TSIFT Mk2 instrument whilst the lowest $D_e = 1.65$ is for the latest TS50 instrument. This means that diffusion losses of ions along the flow tube in the smaller TS50 instrument are much less than in the larger instruments.

It should be noted here, that the approach outlined above clearly characterises the importance of the fundamental phenomenon of diffusion, but this has to be combined with the separate influence of the varying instrumental parameters like flow tube geometry and pressure. Previously, in the routine analyses carried out using the Mk.l and Mk.2 TSIFT instruments, the D_e values for the precursor ions were derived empirically on the basis of experimental data [6] and kinetic modelling. Typical values used in the software analyses for the hydrated hydronium ions $H_3O^+(H_2O)_{1,2,3}$ at m/z values of 37, 55 and 73 were $D_e(37) = 1.20$, $D_e(55) = 1.31$ and $D_e(73) = 1.66$. The D_e values for all other ions were approximated on the basis of an experimental study [6] as a function of their m/z values as:

$$D_e = 1 + 0.0167(m/z - 19) \qquad (14)$$

Whilst this simple equation has allowed reasonably accurate analyses to be carried out using the Mk.l and Mk.2 instruments, the accuracy of SIFT-MS analyses can now be further improved, in the light of the currently available, more detailed understanding of diffusion as described above and it can be performed for various flow tube configurations.

3.4. Calculation of trace gas concentrations

The general equation used to calculate the concentration of the trace gas molecules [M] in the flow tube is [2]:

$$[\mathrm{M}] = \frac{1}{t_r} \frac{f_{p1} I_{p1}/D_{ep1} + f_{p2} I_{p2}/D_{ep2} + \cdots}{f_{i1} I_{i1} k_1 + f_{i2} I_{i2}((k_1 + k_2)/2)/D_{ei2} + \cdots} \qquad (15)$$

I_{p1}, I_{p2}, etc. are the ion signals of all the product ions (count rates corrected for the detector dead time and for mass discrimination in the analytical quadrupole mass spectrometer; see Section 3.1. above), I_{i1}, I_{i2}, etc. are the signals of the precursor ions (e.g., H_3O^+, $H_3O^+(H_2O)$, etc., again corrected for mass discrimination and dead time), k_1 are the rate coefficients for the reactions of the injected precursor ions with M. The k_2, etc., are the rate coefficients for the reactions of the hydrated precursor ions with M [2], D_{ep1}, D_{ep2}, etc., are the respective differential diffusion enhancement factors from Eq. (13) and t_r is the reaction time from Eq. (7). The auxiliary coefficients associated with the product ions, f_p, are normally 1, but they can be used to treat specific unusual cases, as it will be shown later. The f_i coefficients associated with the precursor ions can be used to account for the complex non-linear kinetics involved in the conversion of the H_3O^+ ions into their hydrates, which occurs simultaneously with diffusion. Traditionally, these coefficients have been empirically set by the operators of the instruments by adjusting the so-called D_{f73} parameter [23]. It is now recommended that when the D_{ei} values obtained from Eq. (13) are used, values of $f_{i1} = 1.0$ and $f_{i2} = f_{i3} = f_{i4} = 1.10$ should be used when all the precursor ions, e.g., $H_3O^+(H_2O)_{0\text{–}3}$, are reactive with the detected compound M (e.g., acetone [7]) or $f_{i1} = 1.0$; $f_{i2} = f_{i3} = 1.05$; $f_{i4} = 1.3$ should be used for the situation where the $H_3O^+{\cdot}(H_2O)_3$ is unreactive with M (e.g., as is the case with both methanol and ethanol [7]). These values have been obtained by the least squares fitting of Eq. (15) to the results of a full kinetic model [22] that includes diffusion. These f values help to reduce the discrepancy in the analysis of these compounds to less than 2%, even when the precursor H_3O^+ signal is mostly converted to its hydrates.

The accuracy of the value of [M] obtained using this approach is not diminished by possible secondary reactions of the product ions (such as the partial conversion of MH^+ product ions to the hydrates), because the count rates of all the product ions containing each particular trace gas molecule, M, are properly included in the numerator of the fraction in Eq. (15). In order to correct for the greater decrease of the precursor ion signal when large concentration of the analyte are present, Eq. (15) is expanded to a logarithmic form:

$$[\mathrm{M}] = \frac{1}{k_1 t_r} \ln\left(1 + k_1 \frac{f_{p1} I_{p1}/D_{ep1} + f_{p2} I_{p2}/D_{ep2} + \cdots}{f_{i1} I_{i1} k_1 + f_{i2} I_{i2}((k_1 + k_2)/2)/D_{ei2} + \cdots}\right) \qquad (16)$$

This equation provides exact results for the case of a single precursor ion specie, but it works well as an approximate empirical correction in general, providing more robust results than Eq. (15). The analysis according to Eqs. (15) or (16) has been called the refined SIFT-MS analysis [22] and has been used routinely in SIFT-MS instruments for a few years (see [2]). Worthy of note is the rigorous test of the consistent results obtained when using the three precursor ion species H_3O^+, NO^+ and $O_2{}^+$ to simultaneously analyse the same samples of several trace gases in dry and humid air (described in detail in [24]) demonstrating that the analysis according to Eq. (16) has systematic error <10%.

When the absolute concentration of a trace gas [M] in the flow tube is calculated according to equation (16), it can be converted to the relative concentration of the trace gas in the air sample, p_M/p_0, from the straightforward consideration of continuous flow dilution of the sampled air (flow rate, Φ_a) into the carrier gas (flow rate, Φ_c):

$$\frac{p_M}{p_0} = \frac{[M]p_0}{n_0 p_g}\frac{T_g}{T_0}\frac{\Phi_c + \Phi_a}{\Phi_a} \tag{17}$$

The physical constants used here are: Loschmidt's number $n_0 = 2.687 \times 10^{19}\,\mathrm{cm}^{-3}$, which provides a reference value of concentration at standard atmospheric pressure, $p_0 = 760$ Torr, and temperature $T_0 = 273.15$ K. The resulting p_M/p_0 ratio can be conveniently expressed in the units of parts-per-billion, ppb, by multiplying by 10^9.

3.5. *Special cases*

Several special analyses are listed here that can be achieved using the same equation, either (15) or (16), just using different rate coefficient and *f* factors that can be included in the kinetic library.

3.5.1. *Water vapour quantification*

Measurement of the relative signal level of H_3O^+ ions to the sum of the count rates of the H_3O^+ ions and its hydrated ions, allows the water vapour concentration in a humid sample to be determined. This is used as a control parameter uniquely in SIFT-MS breath analyses, in particular as a check on the air/breath sample flow rate, since water vapour is known to constitute 5.2–6% of breath for the alveolar interface temperatures between 34 and 37 °C [25]. The calculation relies on the value of the effective two-body rate coefficient, k_1, for the association reaction of H_3O^+ with H_2O, which has the following pressure and temperature dependence:

$$k_1 = k_0\left(\frac{p_g}{0.7\,\mathrm{Torr}}\right)\left(\frac{298\,\mathrm{K}}{T_g}\right)^3 \tag{18}$$

Here $k_0 = 1.3 \times 10^{-11}\,\mathrm{cm^3\,s^{-1}}$, is the k_1 value at a helium pressure of 0.7 Torr at a temperature of 298 K [25]. Using this formulation of k_1 in equation (16), when *m*/*z* 19 is the only reactant ion and *m*/*z* 37, 55 and 73 are the three product ions, directly provides the water vapour concentration in the helium carrier gas, which can be converted to percentage (absolute humidity) in the sample air using Eq. (17). Sample data of these ion signals and the calculated water vapour concentration will be shown in Section 4 below.

3.5.2. *Overlap with isotopomers*

Eq. (16) can be used also in the situation where there is a contribution to a product ion signal at a given *m*/*z* value due to the overlap with the minor isotopomers of larger adjacent signals. Here the appropriate f_p coefficients must be used. As an example, consider the following situation. Breath isoprene (C_5H_8) is best quantified using NO^+ precursor ions, which react with isoprene to produce the parent cation ($C_5H_8{}^+$) at an *m*/*z* value of 68 [26]. This *m*/*z* value coincides with that of the ^{18}O isotopomer of the second hydrate of NO^+, i.e., the $NO^+(H_2O)_2$ variant $H_4NO_2{}^{18}O$ at *m*/*z* 68, which inevitably forms when moist air, and especially breath, is introduced into the carrier gas. Since the ion $NO^+(H_2O)_2$ ion at *m*/*z* 66 can be simultaneously measured in SIFT-MS analyses, then the contribution of its isotopomer to the measured signal at *m*/*z* 68 (entered into the Eqs. (15) and (16) as I_{p1} with $f_{p1} = 1$) can readily be calculated. Thus, the signal of *m*/*z* 66 is included to the numerator as I_{p2} in Eqs. (15) and (16) with a coefficient $f_{p2} = -0.006$ (since the fractional abundance of ^{18}O is 0.002 and the $NO^+(H_2O)_2$ ion includes three O atoms). Similar corrections have to be considered, for example, whenever a product ion is at *m*/*z* values of 39, 57 or 75 when using H_3O^+ as the precursor ion.

3.5.3. *Accounting for reverse reactions*

We have shown [14,27,28] that the analysis of some trace gas species, M, using H_3O^+ precursor ions is unusually complicated, because their proton affinities are close to that for the water molecule. Such is the case for formaldehyde, H_2CO, hydrogen sulphide, H_2S, and hydrogen cyanide, HCN. The essential point here is that when the protonated molecules, MH^+, are formed as the proton is transferred from the H_3O^+ ions to the molecules, M, any water molecules in the carrier gas can react with the MH^+ ions to reform the precursor H_3O^+ ions, when this reverse reaction is only slightly endothermic. This reverse reaction is an obvious complication in the analysis, but it can be accounted for since the chemical thermodynamics are well defined in the truly thermalised SIFT-MS reaction system. We have recently dealt with these special cases in three detailed papers. Fitting of the experimental data shows that to accurately analyse H_2S [27], $f_{i2} = f_{i3} = f_{i4} = 0.15$ must be used in equation (17), for HCN [28] slightly negative values $f_{i2} = f_{i3} = f_{i4} = -0.037$ are required and for formaldehyde [14], $f_{i2} = f_{i3} = f_{i4} = 0$ gives the best results.

4. Example of a calculation

In this section we show a step-by-step calculation of the concentration of the breath metabolite acetone monitored during the analysis of single breath exhalations using the TSIFT Mk.2 instrument referred to in the previous section, as a comparative test of the computational methods described above to obtain absolute concentrations.

The flow tube geometry and the measured critical parameters are: $A = 13.85\,\mathrm{cm}^2$, $l = 34.1$ cm, $T_g = 297.15$ K, $\Phi_c = 57.29\,\mathrm{Torr\,l\,s^{-1}}$, $\Phi_a = 1.65\,\mathrm{Torr\,l\,s^{-1}}$, $p_g = 0.73$ Torr. The data obtained for this analysis are shown in Fig. 4 as time profiles of the count rates recorded at six *m*/*z* settings of the analytical mass spectrometer that are required to quantify acetone using H_3O^+ precursor ions and its hydrates. The actual *m*/*z* values and the numbers of counts per second, *N*, acquired during the alveolar portion of the exhalation are given in Table 2.

The *I* values are the ion signals corrected for mass discrimination according to Eq. (1) using $f_{m1} = 0.0$ and $f_{m2} = 0.0003388$, values determined in a separate mass discrimination characterisation exercise for this particular instrument, and using Eq. (2) with $\tau_d = 0.5\,\mu\mathrm{s}$. Eq. (4) provides a value for $v_g = 5907\,\mathrm{cm\,s^{-1}}$, and Eq. (7) then gives the reaction time $t_r = 3.848$ ms.

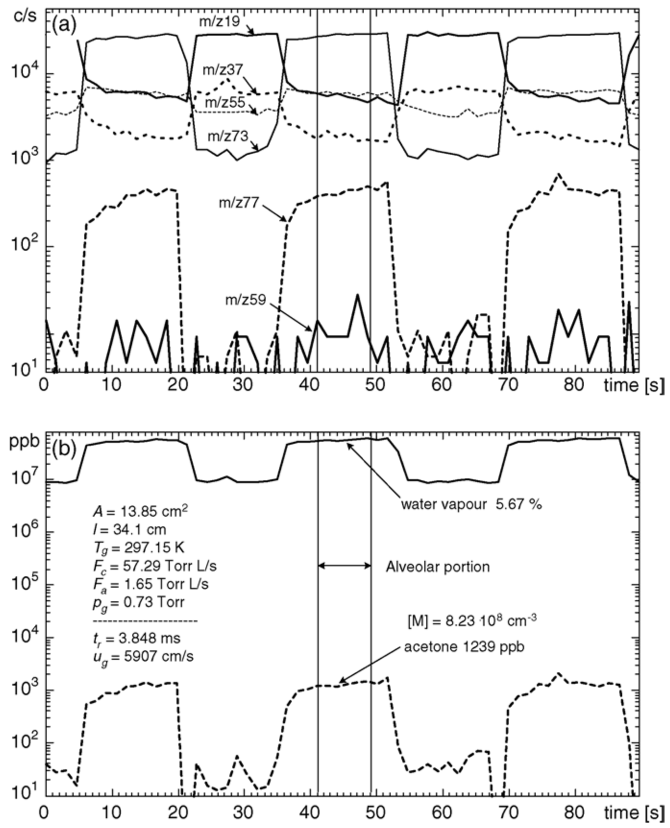

Fig. 4. Time profiles (a) of the ion signals (ion count rates corrected for mass discrimination and dead time) recorded at the *m*/*z* settings given and (b) of the calculated concentrations of acetone and water (in ppb of the exhaled breath) obtained using Eq. (16) from three successive breath exhalations using H_3O^+ precursor ions exploiting SIFT-MS in the MIM mode (see the text). The signal levels used are those in the alveolar portion of the exhaled breath region as indicated by vertical dashed lines.

First it is useful to give an example of the result obtained using the old simplified approximation of the D_e values for this particular instrument by Eq. (14), which is given in Table 2 as $D_{e(old)}$. Eq. (15) can now be evaluated, using the *k* values from Table 1, as:

$$[\mathrm{M}] = \frac{1}{3.848\,\mathrm{ms}}\frac{12.21 + 413.77}{(2.13 + 0.68 + 1.87 + 8.70) \times 10^{-5}} = 8.28 \times 10^8\,\mathrm{cm}^{-3}$$

Table 2

Count rates, *N*; ion signals (corrected for mass discrimination and dead time as described below in text), *I*; and differential diffusion enhancement factors, estimated using the old, $D_{e(old)}$ present $D_{e(new)}$, methods

	m/*z*					
	19	37	55	59	73	77
N	5434	2058	5298	13	22756	373
I	5448.8	2286.3	7644.6	20.0	45759.4	798.3
$D_{e(old)}$	1	1.20	1.31	1.64	1.66	1.93
$D_{e(new)}$	1	1.54	2.05	2.01	2.41	2.4

The ions at *m*/*z* values of 59 and 77 are protonated acetone, $CH_3COCH_3{\cdot}H^+$ and its monohydrate, respectively.

Using the more accurate logarithmic Eq. (16) does not result in a significant change for this trace gas concentration [M], but the difference is discernible as $[\mathrm{M}] = 8.23 \times 10^8\,\mathrm{cm}^{-3}$. Then $p_M/p_0 = 1239$ ppb. In practical software implementation there is no difficulty in using equation (16), and Eq. (15) is only used to make the discussion simpler and more quickly understandable, and also to make the test calculations easier.

However, the approach recommended for future SIFT-MS analyses is to adopt the more precise $D_{e(new)}$ values that have been calculated from the physical properties of the ions using the actual values of D_{1He} given in Table 1. The $D_{e(new)}$ values thus obtained as given in Table 2 are for the conditions (p_g, t_r, Λ^2) in this example. For the calculation of the acetone concentration, the factors $f_{i2} = f_{i3} = f_{i4} = 1.1$ are used in Eq. (16) and the resulting concentration of acetone is $[\mathrm{M}] = 8.35 \times 10^8\,\mathrm{cm}^{-3}$. Then, $p_M/p_0 = 1257$ ppb. Clearly the present new method of calculation reproduces the results obtained by the older analysis very well (to better than 2%) for the particular configuration of the TSIFT Mk.2 instrument. However, the essential point is that our latest approach can be used generally for various sizes of flow tubes, various pressures and various reaction times, whereas the previous older method is not so adaptable. This is an important consideration since new SIFT-MS instruments of smaller size are being developed, which can be used in special situations such as intensive care (therapy) units and general practitioners' surgeries.

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