

The SIFT and FALP techniques; applications to ionic and electronic reactions studies and their evolution to the SIFT-MS and FA-MS analytical methods.

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Abstract.

Flow tube reactors coupled with quantitative mass spectrometry have made, and continue to make, major contributions to gas phase ion-molecule chemistry, to recombination and electron attachment studies and, most recently, to gas phase trace gas analysis. This paper briefly reviews the concepts and principles of operation of flowing afterglow, FA, and flowing afterglow Langmuir probe, FALP, plasma reactors, and selected ion flow tube, SIFT, ion swarm reactors for the study of the above processes. This paved the way to our recent developments of the novel analytical methods that we call selected ion flow tube mass spectrometry, SIFT-MS, and flowing afterglow mass spectrometry, FA-MS. A time line of these developments during the last fifty years is presented. It is shown how exploitation of FA and SIFT has provided the essential kinetics data that allow modelling of the ion chemistry of naturally occurring plasmas, especially the terrestrial ionosphere and interstellar gas clouds, and has greatly facilitated the developments and evolution of SIFT-MS and FA-MS, which are contributing to the science of ambient trace gas analysis. The wide ranging applications of SIFT-MS are alluded to whilst focusing on the successful direct real time quantitative analysis of volatile metabolites in exhaled breath forcibly demonstrating the unique analytical features of SIFT-MS.

Keywords

Flow tubes; Mass Spectrometry; Flowing afterglow; Langmuir probe; FALP; selected ion flow tube, SIFT; selected ion flow tube mass spectrometry, SIFT-MS; flowing afterglow mass spectrometry, FA-MS.

1. Introduction and history.

We first strive to establish the approximate chronology of the development of those fast flow tube techniques that use mass spectrometers as a principal analytical tool. These instrumental techniques were initially conceived for the study of the kinetics of ion-molecule reactions, and subsequently, and importantly, for the study of other reaction processes important in gaseous plasmas, including electron and ion recombination and electron attachment, and, most recently, the development of gas analysis instruments. The intention in this brief summary review is not to produce all-embracing detailed descriptions of these developments, but to focus primarily on those to which the authors together with a few major colleagues have made significant contributions whilst recognising, by appropriate referencing, those researchers in other laboratories who have also made major contributions to this topic.

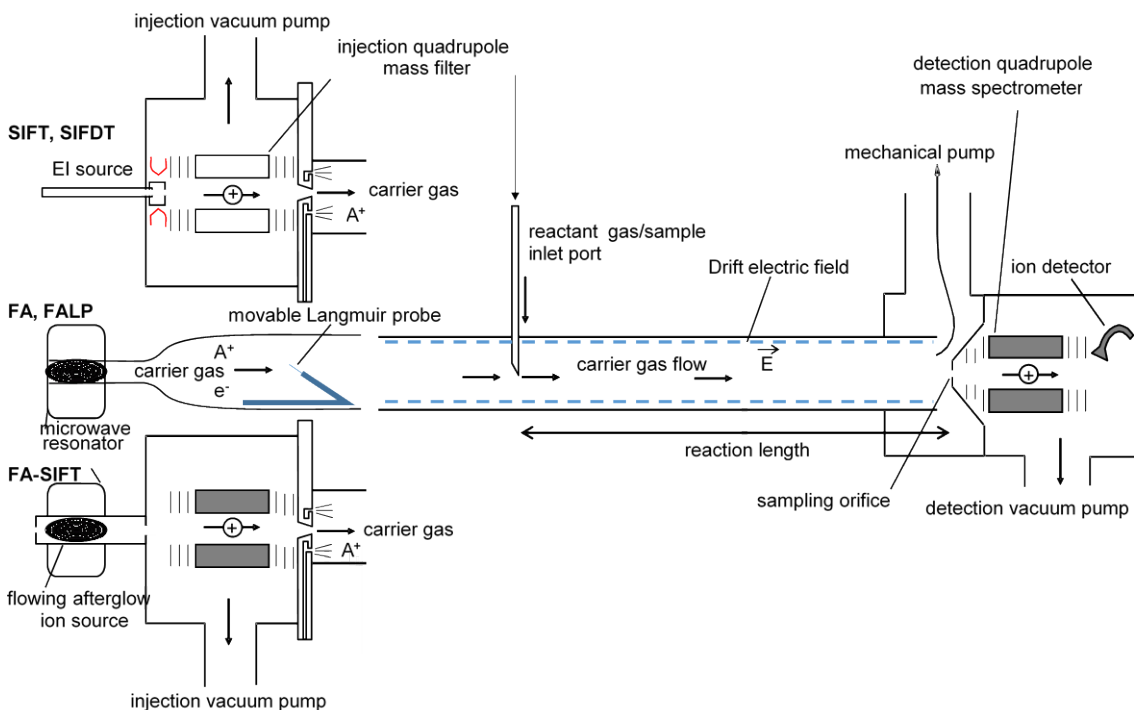


Figure 1. Variants of flow tube systems that exploit quantitative mass spectrometry. Included are representations of the flowing afterglow, FA, and its extension to a flowing afterglow Langmuir probe, FALP, system, the selected ion flow tube, SIFT, and its extension to the selected ion flow drift tube, SIFDT, by establishing an electric field, E , along the flow tube axis, and the combination of an FA ion source with a SIFT to extend ion-molecule reaction studies to a wider variety of positive and negative ions beyond those attainable using the electron impact, EI, source and the microwave discharge source, as indicated. Implementation of variable temperature flow tubes have realised VT-SIFDT and VT-FALP instruments by which ionic and electronic reaction processes have been studied over significant temperature ranges.

The first major development of flow tube methods was the flowing afterglow plasma, FA, in Boulder, Colorado, USA by E.E. Ferguson, F.C. Fehsenfeld and A.L. Schmeltekopf in 1964 [1, 2] to study thermal energy ion-molecule reactions, work which followed the earlier work on the stationary afterglow plasma to study such reactions [3, 4]. The success of this FA method is legendary, as is described in the paper by V.M. Bierbaum in this Special Issue of the *International Journal of Mass Spectrometry, IJMS*, and to which we allude later in this paper. For some ten years EEF, FCF and ALS, together with D.L. Albritton and M. McFarland, also developed the flow-drift tube, FDT, technique by which ion-molecule reactions could be studied over a range of ion-molecule interaction energies [5, 6]. The seminal work of these authors in their Boulder laboratory dominated the study of thermal and near-thermal energy positive ion and negative ion reactions for about a decade, providing a wealth of fundamental data on these reaction processes and much of the kinetics data that largely describes the ion-molecule chemistry of the terrestrial ionosphere [7, 8]. Following the development of the selected ion flow tube technique, SIFT, (see below) it was quickly adopted in Boulder (as a natural replacement for the FA) where it was vigorously exploited for further extensive studies of ion-molecule reactions. Subsequently, the selected ion flow-drift tube, SIFDT, was also developed in Boulder [9] as a replacement for the FDT and, somewhat later, the selected ion drift tube, SIDT, was developed in Innsbruck, Austria [10]. A montage of flow tube schematics, which indicates the essential features of the FA and SIFT and their variants, is shown in Figure 1 instead of separate schematics of each of these instruments. A general feature of these various instruments has been their relatively long flow tubes, typically of 50 to 100 cm. The most recent development in the UK and the Czech Republic has been that of very short flow tubes (about 5 cm long), which are successfully implemented in the SIFT-MS analytical instrument, as described later in this paper.

In 1976, the selected ion flow tube, SIFT, was introduced by N.G. Adams and D. Smith in Birmingham, UK [11]. In the SIFT the ions whose reactions are to be studied are generated in a remote ion source and injected via a quadrupole mass filter into fast flowing carrier gas. This approach avoids the inevitable complications inherent in FA reaction studies in which the ion source gas is inevitably present in the reaction region. Thus, in the SIFT, a wide variety of ions selected according to their mass-to-charge ratio, m/z , can be injected into flowing inert gas and their reactions studied with a range of molecules at thermal energies, including reactions that are judged to be important in naturally occurring media such as the terrestrial ionosphere [12, 13], other planetary atmospheres [14, 15] and interstellar gas clouds [16-19]. Thus, the SIFT technique greatly extended the study of ion-molecule reactions to include those that could not be studied using the FA. The essential features of the SIFT technique will also be alluded to later together with examples of the fascinating and valuable data that have been obtained, especially in relation to ionospheric and interstellar chemistry. Subsequently, both the variable temperature VT-SIFT [20] followed shortly by the variable temperature VT-SIFDT [21] were introduced at Birmingham. The use of these two instruments enabled ion-molecule reactions to be studied over ranges of both gas temperature and ion-molecule interaction energies [22].

A concomitant important advance, also in Birmingham, UK, in 1975 by D. Smith and colleagues, was the creation of the flowing afterglow Langmuir probe, FALP, technique [23], which built on the earlier detailed application of the Langmuir probe to the study of stationary afterglow plasmas by D. Smith, I.C. Plumb and N.G. Adams [24-27] and subsequently for flowing plasmas by P. Spanel [28]. This FALP development also necessarily exploits mass spectrometry (and sometimes optical spectroscopy), and has allowed parallel detailed studies of the other essential reaction processes that occur in gaseous plasmas, including recombination and electron attachment reactions (see later). The subsequent development of the variable temperature VT-FALP allowed measurements of the temperature dependence of the rates of the above reaction processes [29].

The most analytically important development stemming from SIFT is that of selected ion flow tube mass spectrometry, SIFT-MS, by P. Spanel and D. Smith in 1995 [30-35]. This is a novel gas phase analysis method by which trace gases can be quantified in real time in dry air and, significantly, in humid air such as exhaled breath and the headspace of aqueous liquids. SIFT-MS offers a unique contribution to ambient analysis with applications in medicine, environmental science and many other areas [36, 37], as discussed later. Like the SIFT, it can also be utilized to study fundamental ion-molecule reactions and thus has been exploited to expand the kinetics library needed for SIFT-MS gas phase analysis [36, 37].

The conventional flow tubes used in most SIFT instruments worldwide were (and remain) relatively long (typically one metre) and have associated large pumping systems. Thus, they are strictly laboratory based and immobile. Recognising the need for smaller portable devices that could still achieve accurate gas analysis in real time, especially of exhaled breath, and which could be used for onsite analysis within hospital and factory environs, SIFT-MS was developed with more appropriate-sized instrumentation. The first such instrument was created in 1997 having a 40 cm long flow tube, the so-called TSIFT [38-41]. The current SIFT-MS instrument built and commercialised in the UK in 2006, the *Profile 3*, has a very short (typically a few cm) flow tube and much smaller associated pumping systems [36, 42]. This much lighter instrument is now a valuable portable analytical device for real time, on-line ambient gas analysis, including breath analysis and, to state again, it can also be used very effectively for the study ion-molecule reactions. Shortly afterwards, the New Zealand company Syft Technologies Ltd. also produced a SIFT-MS instrument that they have successfully commercialised under a trademark Voice 100 [43]. Concomitant with these advances was the unique development of the flowing afterglow mass spectrometry analytical technique, FA-MS, by which the deuterium abundance in water vapour can be determined [44] even in single breath exhalations in real time, which was aimed primarily at the determination of total body water in patients with chronic kidney disease. Both SIFT-MS and FA-MS can be used for deuterium analysis of water vapour, as alluded to later.

Concomitant with these developments, a similar analytical technique called proton transfer reaction mass spectrometry, PTR-MS, was developed by W. Lindinger and colleagues in Innsbruck, Austria in 1995 [45]. PTR-MS has the form of a flow-drift tube

reactor and built on the expertise gained in Boulder and Birmingham on the FDT and SIFDT techniques, as referred to above. The differing features of PTR-MS and SIFT-MS have been discussed recently in two review papers [46-48].

This short paper is firstly a retrospective of the above developments of flow tube mass spectrometry that shows the linkage between the FA and FALP afterglow plasma techniques, takes a close look at the ion swarm SIFT technique and the applications of these to the study of gas phase reaction kinetics. Secondly, it is a forward look towards the continuing development and growing importance of the newest flow tube/mass spectrometry techniques, the SIFT-MS and the FA-MS analytical methods. SIFT-MS especially is shown to have wide analytical applications in physiology and medicine, environmental monitoring, food science and other areas, as will be referred to at the appropriate places in this paper but using breath analysis as the most exciting exemplar. A timeline of these flow tube mass spectrometry developments is shown in Figure 2. The separate phases of this extensive development will now briefly be described together with some of the notable successes of each instrumental method in promoting the understanding of ionic and electronic reactions and for gas phase analysis of humid air and exhaled breath.

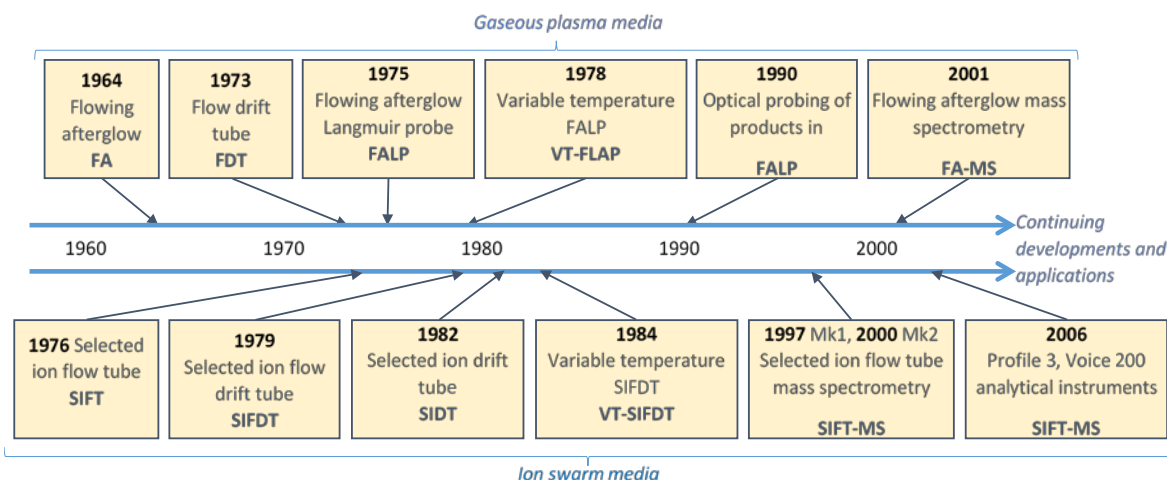


Figure 2. A timeline that indicates in the upper group the development of the flowing afterglow plasma technique, FA, and its variants, and in the lower group the selected ion flow tube, SIFT, ion swarm technique and its variants, including those with embedded electrostatic drift fields. All these techniques involve quantitative mass spectrometry as the essential diagnostic and have been vigorously exploited to study ion-molecule reactions at thermal and near-thermal energies. The inclusion of Langmuir probes into the FA created FALP instruments, which have been used to study recombination and electron attachment reactions at thermal energies. Strictly, the FDT included in the plasma group involves an ion swarm reactor that is formed by isolating ions from the gaseous plasma created in the flowing carrier gas. The latest developments see the creation of the novel selected ion flow tube mass spectrometry analytical method, SIFT-MS, by which ambient gas analysis can be realised obviating sample preparation and flowing afterglow mass spectrometry, FA-MS, for isotopic analysis of water vapour.

2. The FA and FALP plasmas; basic principles and notable successes.

The flowing afterglow plasma, FA, as developed for the study of ionic and electronic interactions, is a gaseous plasma medium in which positive ion numbers are balanced by electrons and/or negative ions to form a quasi-neutral medium. The term afterglow relates to the situation whereby the charged particles, as usually produced in a gas discharge upstream in a flowing inert gas that often contained a trace ion source gas, are decoupled from the ionisation source as they move (flow) away from the discharge region and “cool” by collisions with the abundant atoms or molecules of the flowing carrier gas. Yet, importantly, other unwanted (impurity) neutral and ionic species other than those under study are often generated from the composite ion source gas in the discharge, and these are inevitably transported into the afterglow to complicate the reactions under study, such being avoided in the SIFT technique, as described later. Nevertheless, with careful aforethought, the FA can be used to study interaction and reactions between charged particles (ions and electrons) and those neutral molecules that are introduced downstream into the flowing plasma. The FA is the direct analogue of the earlier pulsed, time resolved or stationary afterglow plasma, SA, in which cooling of the charged plasma particles occurs in the time period following a short pulse of energy from which the plasma forms [49-51]. The primary monitoring device in the FA is the downstream mass spectrometer; it is used to measure the count rates of the primary reactant ions and the product ions of the reactions that occur in the afterglow plasma from which rate constants and ion product distributions are derived. Much has been written about the physics involved in the formation of afterglow plasmas, but this has been discussed in detail in the pioneering FA papers [1, 2] and need not be reprised here. The essential point is that kinetics data can be obtained for reaction processes occurring between charged and neutral particles possessing Maxwellian speed distributions for which a temperature can be designated. Such is appropriate to some naturally occurring plasmas such as the lower terrestrial ionosphere and dense interstellar gas clouds.

The driving force for creating the FA by Ferguson and colleagues was their interest in terrestrial atmosphere ion chemistry and the study of the basic ion-molecule reactions that produce the ions observed in the ionosphere [7, 8, 13]. Their imaginative and energetic approach resulted in the major contribution to this science in the 1960s and early 1970s, as reviewed in a chapter in a book on ion chemistry [52]. In a nutshell, the ion chemistry of the upper ionosphere was shown to involve the reactions of relatively simple atomic and diatomic positive ions (largely formed by solar photon ionisation) with atmospheric neutral atoms and molecules that leads to the production of, for example, the NO^+ ions observed in these regions. This molecular ion can rapidly recombine with the free electrons thus controlling and limiting the plasma (positive ion/electron) number densities. This simple plasma chemistry is represented in the scheme shown in Figure 3 [19]. It should be noted that the “terminating ions” NO^+ and O_2^+ are relatively unreactive with the major neutral components of air and, as we state later, are ideal reagent ions for chemical ionisation as exploited in SIFT-MS (see later).

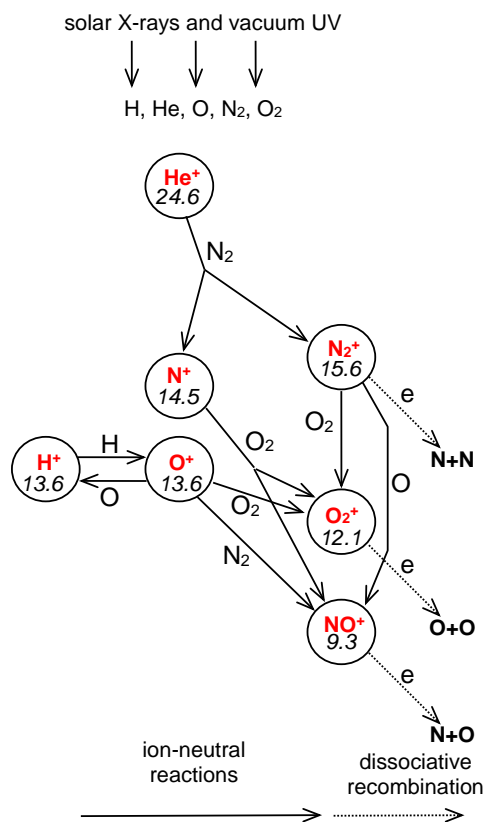


Figure 3. Ion chemistry of the upper atmosphere (the thermosphere). The ionic species (inside the circles) are arranged from the top to the bottom of the diagram in order of their reducing recombination energy (given in electron volts for each ion). The solid arrows indicate the binary ion-neutral reactions that are occurring (with the neutral reactants indicated along the arrows), and the dashed arrows indicate dissociative electron-ion recombination reactions. Reproduced from [19] with permission from John Wiley & Sons, Inc.

The ion chemistry of the lower ionosphere, which involves complex ions and molecules and the formation of adduct or cluster ions (see Figure 4), is much more challenging to study experimentally in the FA, but the difficulties were alleviated by the appearance of SIFT, as discussed later.

The flowing afterglow Langmuir probe, FALP, instrument was a major development, by Smith and colleagues in Birmingham that involved the inclusion of a Langmuir probe into a standard FA system, to measure the local electron and ion number densities along the quasineutral gaseous plasma column [23, 53]. The major objective of this development was to study recombination and attachment reactions at thermal energies, reactions that inevitably occur in laboratory and naturally occurring gaseous plasmas, such as those included in the schemes in Figure 3 above and in Figure 4 that are discussed later. There was a serious dearth of kinetic data on these processes that was having an inhibiting effect on the production of meaningful and reliable ion-chemical models of naturally-occurring plasmas in which there was considerable interest at that time. By the time of this FALP development, the measurement of electron number

densities in active electric discharges (high electron temperatures) using Langmuir probes already had a long history [54], but measurements in low temperature thermalized afterglow plasmas are more challenging and so much effort had to be given to this problem before the Langmuir probes/FA combination could be used with confidence [55]. Detailed studies had already been carried out at Birmingham to combine Langmuir probes with pulsed stationary afterglows [24, 56] and the knowledge gained was crucial in the rapid incorporation of these probes into the flowing afterglow. However, a Langmuir probe had to be engineered that could be moved smoothly along the (100 metre long) axis of the FA plasma to measure the gradient of electron/ion densities in the quasineutral plasma. From the derived rate-of-loss of the electrons/ions (knowing the plasma flow speed), recombination and attachment rate coefficients could be derived. This procedure was later extended to measure the ion number density gradient in ion-ion plasmas [53, 57]. As usual, the downstream mass spectrometer is exploited to monitor the positive and negative ions in the plasma. Hence, the FALP provided a versatile method for the study at thermal energies of positive ion-negative ion mutual neutralisation [29, 53, 57-59], electron-ion recombination [60-70], and electron attachment to form negative ions [71-76].

The extensive FALP studies of these processes represented major contributions to the understanding of the fundamentals of these reactions and the essential data for the ion/electron and ion/ion rate coefficients needed for chemical models of the terrestrial ionosphere where dissociative recombination, ion/ion mutual neutralisation and electron attachment to form negative ions occurring (see Figure 3 and Figure 4). This and also the involvement of recombination processes in interstellar gas clouds, will briefly be described in later sections of this paper. Since the gas, electron and ion temperatures can vary widely in these regions, and the rates of the reaction processes often depend on these temperatures, the variable temperature VT-FALP, was developed using which the temperature dependence of dissociative recombination and electron attachment reactions have been studied, under truly thermalised conditions and also at elevated electron temperatures [62, 77-82]. An especially detailed study over two decades has been that of the electron recombination of H_3^+ ions, which has great significance in the ion chemistry of interstellar clouds [63, 68, 69, 83-85]. The neutral products of electron-ion dissociative recombination reactions that have also been studied in FALP exploiting a combination of laser fluorescence and vacuum ultraviolet spectroscopy [64]. The challenging and successful FALP study of the absolute rate coefficient for electron attachment to the C_{60} molecule is particularly interesting and unique [79, 81, 86, 87].

It is rewarding to report that the FALP method continues to be profitably utilized in other laboratories for the study of these reaction, especially for electron-ion recombination, principally by N.G. Adams and colleagues [88-90] and J. Glosik and colleagues [84, 85], and for electron attachment, principally by T.M. Miller and colleagues [91, 92], in response to the need of more kinetic data for ion-chemical modelling of naturally-occurring plasmas [93, 94].

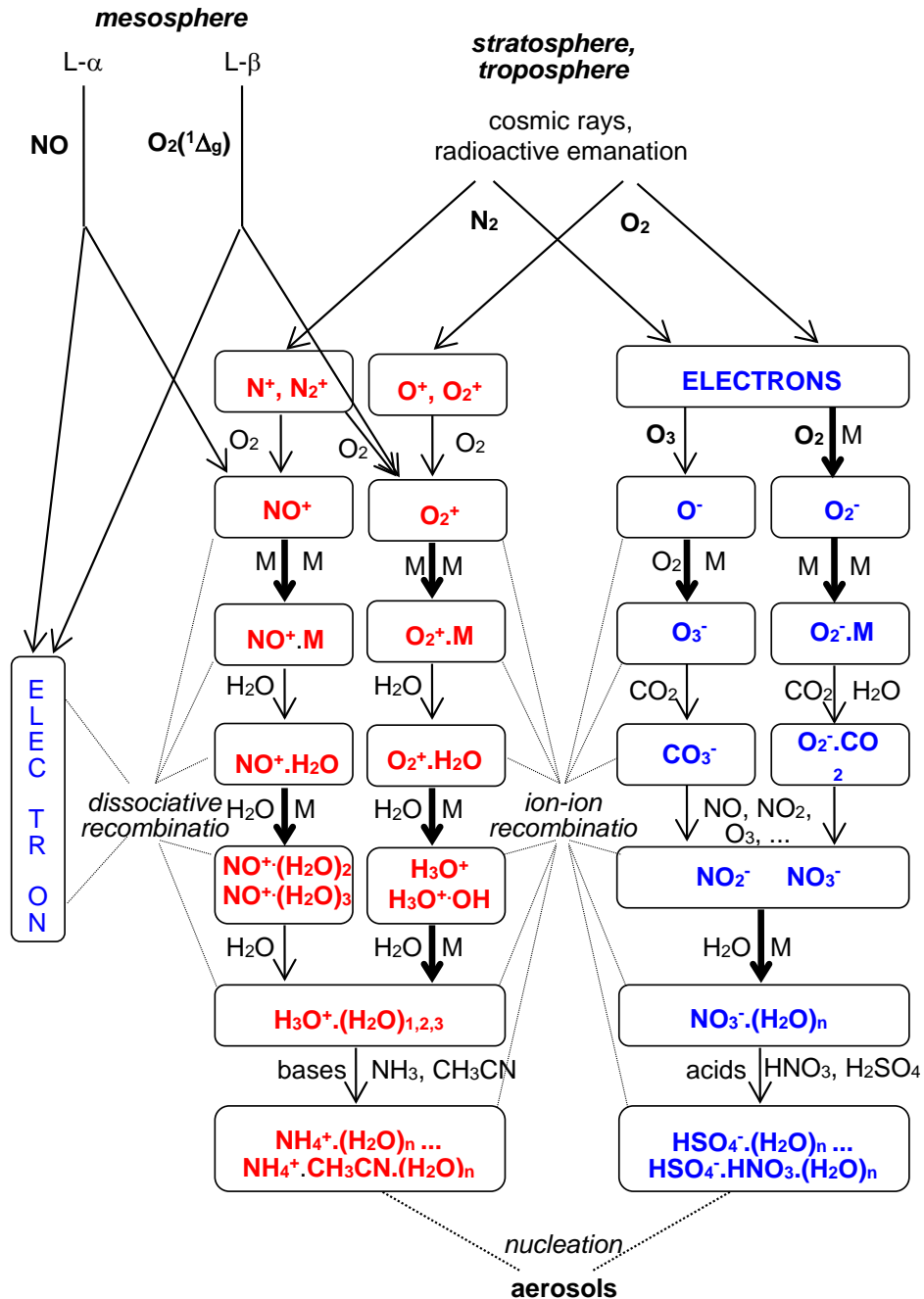


Figure 4 The positive (*left*) and negative (*right*) ion chemistry of the lower atmosphere (the mesosphere, the stratosphere and the troposphere). Binary ion-molecule reactions and electron attachment reactions are indicated by thin arrows, ternary ion-molecule reactions are indicated by thick arrows with M representing the third body (N₂ or O₂). The neutralisation processes of electron-ion (dissociative) recombination and ion-ion recombination are indicated by dashed lines. Note the different sources of ionisation in the different regions of the lower atmosphere indicated in the uppermost part of this scheme. The terminating ions in the mesosphere are of the type H₃O⁺(H₂O)_{1,2,3} and NO₃⁻(H₂O)_n, whilst the ion chemistries of the stratosphere and the troposphere progress further into the more complex ions indicated in the lowest part of this scheme. Reproduced from [19] with permission from John Wiley & Sons, Inc.

3. SIFT and SIFDT ion swarm techniques; notable successes.

Modifications by the Boulder group to the conventional FA described previously, enabled positive and negative ions in the ion swarm to be propagated downstream from the carrier gas discharge. This modification is notable in that it essentially avoided the undesirable constraints imposed by the quasineutral gaseous plasma FA medium. Importantly, single charge ion swarms devoid of free electrons also allowed the introduction of an electric field in the flowing gas to create **a flow/drift tube** by which ion-molecule reactions could be studied as a function of the ion-molecule interaction energy.[5,6]. The initial **FDT** studies provided much data on the mobility of ions in gases, as are required for drift tube kinetics studies [95].

However, the real breakthrough in ion-molecule kinetics studies was the introduction of **the selected ion flow tube, SIFT**, technique [11]. This involved the creation of ions in a remote electrical discharge or an electron impact ion source and the selection of the ion specie of interest (from a mixture) according to its mass-to-charge ratio, m/z , using a quadrupole mass filter. Thus, a current of ions at a given m/z can be injected at low energy (inhibiting collisional dissociation) into a fast-flowing inert carrier gas (usually helium), these translationally-energetic ions thermalizing in collision with the carrier gas atoms/molecules producing a thermalised ion swarm at the temperature of the carrier gas [11, 22]. This provided a facility to determine the rate constants and product ions for the reactions of a very wide variety of ions with numerous neutral molecules, as highlighted below. After the real value of the SIFT for the study of both positive ion and negative ion reactions with atoms and molecules had been established, a variable temperature version, the VT-SIFT [20], was created in Birmingham. This was made even more versatile by the inclusion of a drift tube, thus creating the variable temperature selected ion flow drift tube, VT-SIFDT [21, 96].

The value of the SIFT vis-à-vis the FA for the study of ion-neutral reactions are several fold. Ions of interest can be created from a suitable gas or vapour that is excluded from the carrier gas, a most important feature because the presence of source gases in the reaction region can seriously complicate reaction studies and data interpretation almost to the point of impossibility. SIFT also provides a facility to study the reactions of a wide variety of very reactive ions, and series of ions, e.g. CH_n^+ , H_nO^+ , NH_n^+ can be studied that are often involved in the complex ion chemistry of ionized gaseous media, such as interstellar clouds (see below). Further to these advantages, the sampling of ions from a neutral gas, rather than gaseous plasma, is simple and can be accurately quantitative, which is a very important feature when using SIFT-MS as a quantitative analytical tool, as described later. Using the SIFT, the rate constants and product ions of numerous ion-molecule reactions have been determined as summarised in several review papers [37, 97, 98]. Such kinetics data are essential for ion-chemical modelling of natural plasmas and also for the kinetics database required for SIFT-MS gas analysis.

Following the inception of the SIFT it was quickly adopted in other laboratories. In the Boulder laboratory a SIFDT [9] instrument was realised, which greatly extended the studies of the energy dependence of the rate coefficients and product ion distributions for

both positive ion and negative ion reactions with molecular and atomic neutrals [7, 8]. These SIFT and SIFDT developments accelerated gas phase ion chemistry studies and especially the understanding of such reactions occurring in lower terrestrial ion chemistry [8]. The complexity of this ion chemistry is illustrated by the partial scheme shown in Figure 4, where the development of the complex ions in this region of the atmosphere involves chains of both positive ion and negative ion reactions and where electron-positive ion and positive ion-negative ion mutual neutralisation reactions continuously intervene. It is noteworthy that the H_3O^+ and its hydrates are relatively unreactive in atmospheric air, which is exploited in SIFT-MS where H_3O^+ is adopted as a valuable reagent ion. Electron attachment reactions involving simple and complex neutral species in the gas phase (and to some extent on particle surfaces) are the source of the free negative ions observed by rocket-borne mass spectrometers in these lower atmosphere regions. These complex reaction schemes can be made semi-quantitative using the considerable body of kinetics data provided by the many SIFT [37, 99, 100] and FALP studies [19, 88].

A most valuable application of the SIFT and its variants is in the field of interstellar ion chemistry that involves many unstable, very reactive ions. A wide variety of organic molecules are observed in diffuse and especially dense molecular clouds together with some positive ion species [18, 19]. All these neutral and ionic species must originate from H, N and O atoms and H_2 molecules and gas phase ion chemistry is initiated following their ionisation by interstellar electromagnetic radiation and galactic cosmic rays, which ultimately produces many of the observed polyatomic molecules. This complex ion chemistry involves parallel and sequential ion-molecule reactions, again involving concomitant electron-ion dissociative recombination neutralization reactions. A sense of the complexity of this ion chemistry can be seen in Figure 5 [19]. To trace this complex ion chemistry it has been necessary to investigate the reactions of several series of ions of the kind CH_n^+ ($n = 0-5$) and NH_n^+ ($n = 0-4$) with a wide variety of inorganic and organic neutral molecules at appropriate temperatures [101, 102]. These investigations could not have been successfully performed without the SIFT and VT-SIFT instruments since, uniquely, ions in these series can readily be produced in a remote ion source, individually injected into the SIFT helium carrier gas and their reactions studied. Such is not possible using FA methods.

Using these SIFT ion-molecule kinetics data, the dissociative recombination coefficients and the neutral products of such recombination reactions, much determined using the FALP technique [64, 68], and by clever ion-chemical modelling, the overall aspects of the ion chemistry of diffuse and dense interstellar clouds has been elucidated. A particularly interesting discovery was the apparent involvement of the closed shell ion CH_3^+ in the production of several of the observed polyatomic neutral molecules present in dense interstellar clouds. This involved the radiative association of CH_3^+ with other known interstellar molecules such as H_2O and NH_3 , which results in the adduct ions CH_3OH_2^+ and CH_3NH_3^+ . The radiative association reaction rates required in the ion-chemical modelling that explain the appearance of complex neutral molecules in dense interstellar clouds were derived from the analogous three-body association reactions determined in SIFT and VT-SIFT experiments [103]. These adduct ions CH_3OH_2^+ and

CH_3NH_3^+ recombine dissociatively to partially produce CH_3OH (methanol) and CH_3NH_2 (methylamine), both known interstellar molecules. These and other reactions involved in interstellar molecular synthesis are illustrated in Figure 5. Detailed schemes of this and other interstellar ion chemistry are summarised in review papers [18, 19, 94, 104].

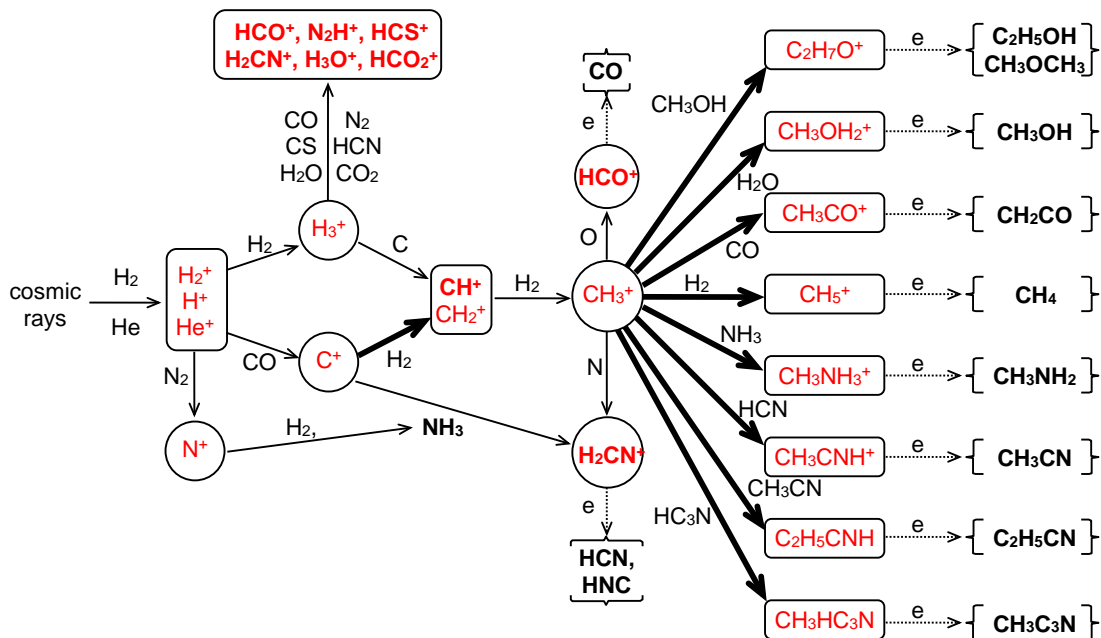


Figure 5. The initial reactions and some radiative association reactions that are involved in the ion chemistry of dense interstellar clouds and which lead to the synthesis of the carboxy, cyano and amino molecules shown. The binary ion-molecule reactions are indicated by thin arrows, the radiative association reactions are indicated by thick arrows, and the dissociative recombination reactions are indicated by dashed arrows leading to the neutral molecules inside the compound brackets. The molecules indicated in bold type are known (observed) dense cloud interstellar molecules. Note the central role of CH_3^+ ions in this chemistry. A sequence of reactions is involved in the synthesis of NH_3 from N^+ ions. Reproduced from [19] with permission from John Wiley & Sons, Inc.

With the subsequent development of the VT-SIFDT [21, 96] it was possible to study ion-molecule reactions over a range of gas temperatures and ion interaction energies. Thus, reactions of perceived interstellar significance could be studied at temperatures closer to those pertaining to dense interstellar clouds [105]. A particularly successful and illuminating study was that of isotope exchange in ion-molecule reactions, which are driven by zero-point-energy differences between the reactants and products, reactions which become more significant at low reaction temperatures [106]. The detailed studies of isotope exchange reactions are summarised in [107]. Thus, it is seen that the abundance of heavy stable isotopes of some elements, including ^{13}C and ^2H , are apparently fractionated into some interstellar molecules present in cold interstellar clouds [108]. To produce persuasive ion-chemical models of this phenomenon [109], kinetic data on isotope exchange reactions were required. These were provided by a series of VT-SIFDT measurements in which the kinetics of some key isotope exchange reactions could be studied in both the forward and reverse directions. These studies included the

key reactions $^{13}\text{C}^+ + ^{12}\text{CO} \leftrightarrow ^{12}\text{C}^+ + ^{13}\text{CO}$ [108], $\text{H}_3^+ + \text{HD} \leftrightarrow \text{H}_2\text{D}^+ + \text{H}_2$ [20, 110] and $\text{CH}_3^+ + \text{HD} \leftrightarrow \text{CH}_2\text{D}^+ + \text{H}_2$ [106]. Such studies provided the thermochemical data by which it was confirmed that isotope exchange/fractionation in ion-molecule reaction does occur at increasing rates as the temperature decreases towards those pertaining to interstellar clouds.

SIFT and its variants remain important instrumentation for the study of ion-molecule reactions. Various forms of ion source have been used in SIFT instruments to provide a variety of reactant ions, including cluster ions [111]. A special mention is due to the developments by C.H. DePuy and V.M. Bierbaum in Boulder, by the development of the tandem FA/SIFDT instrument which provides high sensitivity, high resolution and chemical versatility by integrating a flowing afterglow ion source [112] into their SIFT system, which provided a wide range of complex primary ions, including negative ions, using which they have carried out comprehensive studies, including isotope exchange in ionic reactions [113-116]. Additionally, they upgraded the downstream analytical mass spectrometer to include MS/MS for more certain product ion identification. These developments have promoted gas phase ion-molecule chemistry to a higher dimension than is possible by only utilising basic FA and SIFT instruments.

4. Selected ion flow tube mass spectrometry, SIFT-MS.

Chemical ionisation, CI, is a well-recognised and a well-used approach to non-destructive ionisation in mass spectrometry, especially of complex molecules that always partially fragment under electron ionisation. Thus, electron ionisation of complex mixtures of humid air and trace compounds, such as exhaled breath and other biogenic media, results in very complex mixtures of ions. Such a complication can be diminished using some form of extraction and gas chromatographic separation (GC-MS), but this cannot realise a real time analytical technique. Recognising a growing interest in breath analysis for clinical diagnosis and therapeutic monitoring, D. Smith and P. Spanel saw the potential value of CI and SIFT for the **real time** analysis of complex gaseous media; thus the unique new analytical technique called selected ion flow tube mass spectrometry, SIFT-MS, was born [30-35]. SIFT-MS is an ideal ambient analysis method that is utilised for the immediate real time analysis of humid air obviating sample collection and treatment, such as water vapour removal or pre-concentration of trace compounds that is usually required for GC-MS analysis and which can compromise the sample to be analysed. Thus, data acquisition and analysis by SIFT-MS are rapid and reliable, which is particularly important for breath analysis in the clinic.

SIFT-MS essentially is an inversion of the SIFT technique in that if the rate constant for the reaction of a particular precursor ion with a compound M is known, then that reaction can be exploited to determine the concentration of the analyte gas [M] present in the helium carrier gas of a flow tube reactor. Thus, by determining the count rates of both the reagent (precursor) ions and the characteristic analyte (product) ions of the analytical reaction by the downstream analytical mass spectrometer of a SIFT-MS instrument (Figure 6), the concentration of analyte molecules [M] can be determined [47, 117]. If a mixture of several analyte gases is introduced into the carrier gas simultaneously, the

reduction in the count rate of the reagent ions will reflect the net effect of the reactive loss due to all the individual analyte gases and so analysis of individual composite compounds cannot be achieved by simply recording the decrease of the reagent ion signal. However, if the reactions of each reactant gas with the chosen reagent ion result in different and unique characteristic analyte ions, then their m/z values and their individual count rates will identify and allow quantification of the individual neutral analyte compounds in the mixture [118, 119]. Thus, SIFT MS analyses are based on the measurements of precursor (reagent) and product (analyte) ion count rates at the downstream mass spectrometer detection system. This provides real-time simultaneous quantifications of trace gases in complex mixtures such as exhaled breath, the headspace above urine and cell and bacterial cultures and other media, as illustrated in Table 1.

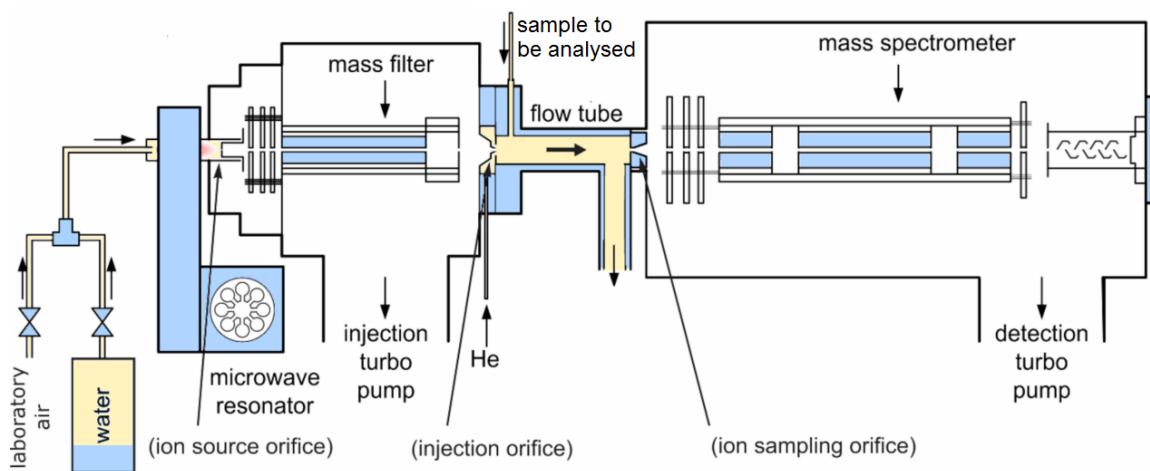


Figure 6 A schematic of a *Profile 3* SIFT-MS instrument. Reagent ions generated in the microwave discharge are extracted via the ion source orifice, selected by the injection mass filter, pass into the flow tube and react with the trace gas analytes in the sample gas. Reagent and characteristic product (analyte) ions are analysed using the downstream quadrupole mass spectrometer, which realises real time analyses of the composite compounds in an air or exhaled breath sample.

An important point to appreciate is that only a few reagent ion species are suitable for SIFT-MS analyses of air and breath. It turns out that H_3O^+ , NO^+ and O_2^+ are the most suitable reagent ions, because they do not react rapidly with the major components of air and breath, viz. N_2 , O_2 , H_2O , CO_2 and Ar, but they do react rapidly with most volatile organic compounds (VOCs) to produce product ions characteristic of the various neutral molecules, M, in an air sample being analysed [36]. Extensive SIFT studies of the reactions of the three suitable reagent ions have been carried out under well-controlled thermalised conditions at 300 K carrier gas temperature to provide the rate constants for the analytical reactions and also identify the characteristic product ions that allow unambiguous analyses of trace gas components of gas mixtures. When humid air or breath is analysed, cluster (hydrated) ions such as $\text{H}_3\text{O}^+(\text{H}_2\text{O})_{1,2,3}$, and $\text{NO}^+(\text{H}_2\text{O})_{1,2}$ are inevitably formed from the injected reagent ions [120]; these cluster ions also act as precursor/reagent ions leading to hydrated characteristic analyte ions that must be included in the SIFT-MS analysis.

Other important physical phenomena must be accounted for to achieve accurate analysis, especially the differential diffusion of the lighter reagent and the heavier analyte ions along the flow tube reactor, and mass discrimination in the analytical (quadrupole) mass spectrometer [42, 121]. Detailed studies of these phenomena have been carried out and their descriptive parameters have been parameterized and included in the sophisticated on-board data reduction and analysis software for SIFT-MS [117]. This allows immediate accurate quantification of trace gases in humid air and exhaled breath in times sufficiently short to trace the concentration profiles of metabolites in single breath exhalations, as shown below. A valuable and unique feature that makes data acquisition by SIFT-MS much more efficient than most other analytical techniques is that accurate analyses are obtained without the need for regular calibration using internal or external standards [36, 122]. Such development has been possible due to the detailed understanding of both the physical and ion-chemical processes involved, which has been acquired by the many years of research using the FALP and SIFT plasma and ion swarm techniques, as outlined previously.

Most laboratory-based SIFT instruments, as depicted in Figure 1, are large, heavy (typically 2000 kg) systems with long flow tubes (typically 100 cm) and large pumping systems, which are strictly immobile. When utilised as SIFT-MS systems they can only be used for analysis by transporting gas samples to the instrument. The requirement for on-site analyses in the clinic gave impetus to the generation of a transportable SIFT-MS and this was achieved in stages, firstly with the commercial production in the UK of an intermediate-sized instrument (350 kg; SIFT Mk.1) that demonstrated the feasibility of SIFT-MS for accurate analysis and subsequently the latest commercial *Profile 3* instrument (120 kg) [42], and the *Voice 200* instrument (200 kg) [123] in New Zealand. The unique *Profile 3* has a very short flow tube of length 5 cm [36, 119]. It has a simple microwave cavity discharge ion source [124, 125] to supply the H_3O^+ , NO^+ and O_2^+ reagent ions and small vacuum pumps. The package is easily transportable and has been located in hospitals, clinics and even an operating theatre for the real time analysis of metabolites in exhaled breath [126]. A schematic of this instrument is shown in Figure 6.

The SIFT-MS instruments have been exploited in several laboratories for the analysis of a wide variety of complex gaseous media and vapours, the *Voice 200* in New Zealand [127-129] and Ohio [130, 131], and the *Profile 3* in the Open University, UK [132] and Imperial College London [133]. This is indicated in Table 1 and for more details see [36, 47, 134]. To repeat, collection and pre-concentration of samples can be avoided when sensitivity is not an issue, but many successful studies have also been carried out by using collected bag samples of air and exhaled breath that allow longer integration times [135-139]. But the most challenging analysis is indeed that of real time breath analysis; when this can be achieved, SIFT-MS can be successfully utilized for most of the media included in Table 1.

Table 1 Some studies carried out using SIFT-MS.

Biomedical
Physiology
Urine
Ketones
Volatile markers of ovulation
Breath
Influence of diet on exhaled volatiles
Ethanol metabolism
Oral microflora and difference between nasal and oral exhalations
Exercise
Skin
Release of volatile compounds
Halitosis
Odorous breath compounds
Addiction and substance abuse
Breath composition after Antabuse ingestion
Compounds in tobacco and cannabis smoke
Renal failure
Breath biomarkers of kidney dysfunction
Total body water monitoring
Bacterial infection
Breath biomarkers of infection in cystic fibrosis
Alveolar lavage
Bacterial cultures
Cancer
Urine
Volatile biomarkers of cancer and infection
Breath
Diagnostic breath biomarkers
Tissue cell cultures
Volatile compounds released by cancer cell lines
Diabetes
Breath biomarkers
Inflammatory bowel disease
Breath biomarkers of disease activity
Food science
Quantification of aroma compounds in fermentation
Oil quality
Food flavour analyses
Volatile compounds emitted by fruits and vegetables
Volatile organic compounds related to sensory qualities
Environment; health and safety
Biological monitoring
Exhaust gases
Emissions from waste incineration, sewage and landfills
Security
Detection of volatile markers of explosives
Products and fumes of explosions

The quality of breath analysis that can be achieved with *Profile 3* is shown by the data in Figure 7 for the simultaneous real time analysis of several metabolites in sequential single breath exhalations. Of note is the very wide concentration range of the compounds accessible, from water vapour and carbon dioxide at few percent levels to those of the common breath metabolites acetone and hydrogen cyanide at the few to a few hundred parts-per-billion by volume, ppbv, levels. As can be seen, the reproducibility of the measured concentrations between breath exhalations is also good. The water vapour concentration is, as expected, close to 6% by volume of exhaled air, which reflects the saturation vapour pressure of liquid water at body temperature, and this acts as an internal validation of the instrument set-up, a very valuable feature that is unique to SIFT-MS.

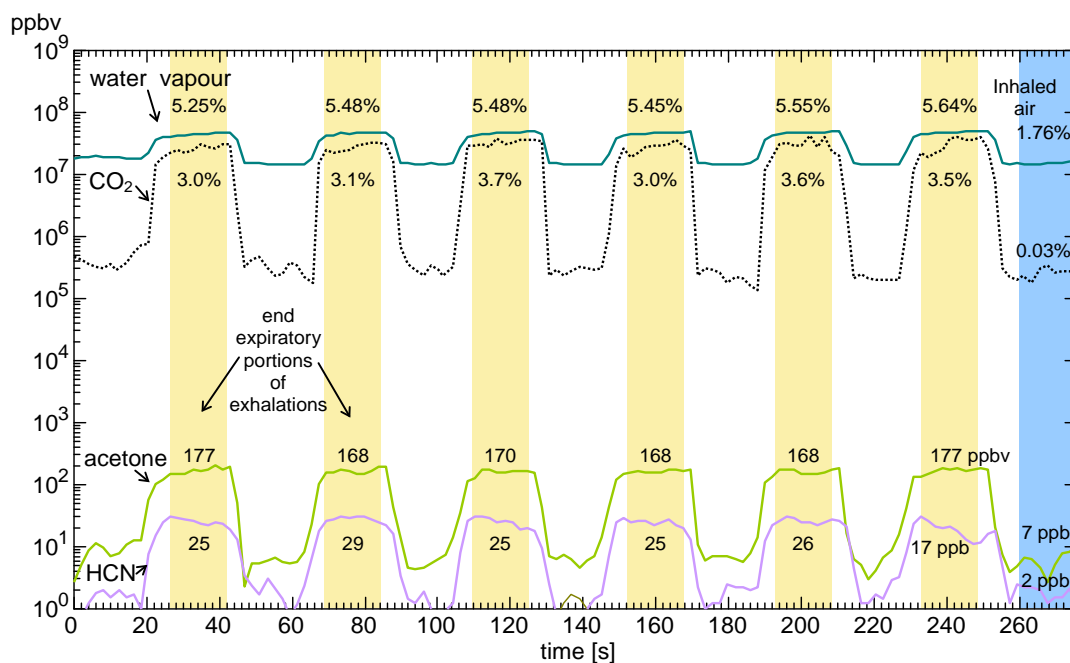


Figure 7 SIFT-MS analyses of time profiles of concentrations of water vapour and CO₂ (in percent, %), acetone and hydrogen cyanide (in parts-per-billion by volume, ppbv), during sequential breath exhalations by a volunteer. A *Profile 3* SIFT-MS instrument was used to obtain these data, which demonstrate the reproducibility of quantification and the dynamic range. The average concentrations in the end-expiratory portions of the exhalations (yellow) are given. Also indicated are the inhaled levels (blue). Reproduced from [47] by permission of The Royal Society of Chemistry.

Using this facility, many studies of exhaled breath have been carried out both as indicators of the variability of trace gas biomarkers in the normal physiological state and of biomarkers of abnormal physiology. These studies, and those of the analysis of other media, are reported in many research papers and summarised in recent review papers [36, 47, 134]. A most exciting example of SIFT-MS analyses involves the recognition and quantification of hydrogen cyanide, HCN, in exhaled breath in healthy persons and of its elevation in the exhaled breath of patients suffering from the debilitating condition cystic fibrosis, CF. This has involved extensive studies of HCN emitted by *in vitro* cultures of the bacterium *Pseudomonas aeruginosa*, PA, in concert with detailed *in vivo* breath

analysis studies of healthy people (controls) and patients with CF. These wide-ranging studies have established HCN as a non-invasive single volatile biomarker of *PA* in the airways of CF patients, as reviewed in a recent paper [140].

A further success of SIFT-MS is its development as a method for on-line, real time quantification of deuterated water vapour in exhaled breath following a small dose (ingestion) of deuterated water, D₂O, by which the total body water, TBW, of an individual can be determined. Whilst isotopic analyses of water vapour can be accurately carried out using SIFT-MS [141, 142], in order to facilitate such analyses in a point-of-care setting, a similar yet simplified and lower cost method called flowing afterglow mass spectrometry, **FA-MS**, has been developed [44, 143]. This exploits an FA plasma to ionise water vapour present in a sample of (partially deuterated) exhaled water vapour or in aqueous liquid headspace (for example of urine or blood) that is introduced directly into the afterglow plasma. Thus, deuterated isotopologues of hydrated hydronium ions are formed, the quantitative mass spectrometric analysis of which provides the concentration of HDO in the water vapour/air/breath sample. By using the principle of isotope dilution together with the quantity of D₂O ingested, the total body water, TBW, of an individual can be determined on-line and in real time by analysing single breath exhalations. Thus, the TBW of several cohorts of patients and healthy controls [144] have been measured in the clinical setting using FA-MS, [44, 145, 146], including patients suffering from chronic kidney disease who naturally suffer from water overload [147-149] and to whom such studies have been especially focused. It has been shown that this FA-MS method of measuring TBW is both feasible in a busy renal unit and acceptable to patients attending the dialysis clinic [150, 151]. Further studies are currently in progress in clinical trials to establish the value of this approach to monitoring body composition and thus avoid the complications of water overload.

5. Summary, future directions and concluding remarks.

Quantitative mass spectrometry continues to have a vital role in ion chemistry and gas phase analysis. It is an essential component in the development of fast flow tubes and flow/drift tubes, FA, FDT, and especially selected ion flow tubes, SIFT and SIFDT. The creation of the latter techniques signalled a rapid increase in studies of gas phase ion-molecule reactions. The FA coupled with the Langmuir probe, FALP, greatly extended the studies of recombination and electron attachment processes that occur in plasmas. The kinetics data these techniques have provided, and continue to provide, are essential for the proper understanding of the ion chemistry of naturally occurring plasmas, especially the terrestrial ionosphere and interstellar clouds and, more recently, other planetary and planetary satellite atmospheres. The recent development of SIFT-MS is making an important contribution to ambient trace gas analysis with its special feature of accurate quantification of compounds in air and aqueous fluid headspace samples, and the non-invasive detection and accurate analysis of metabolites in exhaled breath. These studies are beginning to provide important insights into human and animal physiology in support of clinical diagnosis and therapeutic monitoring. There are few constraints to the application of SIFT-MS in fields where accuracy and precision are not as stringent as in medicine, for example in monitoring food freshness, which is now receiving considerable

attention using SIFT-MS. Similarly, FA-MS has become accepted as a technique for isotopic analyses of water vapour for clinical determination of TBW and for studies of water transport across the peritoneal membrane in peritoneal dialysis patients.

Innovative additions to SIFT-MS analytical instrumentation are also under active consideration, such as the inclusion of switchable drift fields and ion separation by mobility in order to improve ion (and hence compound) identification and quantification. A VT-SIFT is now operational in the Prague laboratory to extend the ion-molecule kinetics studies to those that are considered to be involved in the ion chemistry occurring in the atmosphere of the satellites of the giant planets. Smaller instruments are in the design phase that will be even more readily portable and to have sensitivities below 1 ppbv per second of integration time.

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