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Influence of weakly bound adduct ions on breath trace gas analysis by selected ion flow tube mass spectrometry (SIFT-MS)

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ABSTRACT

This paper describes how weakly bound adduct ions form when the precursor ions used in selected ion flow mass spectrometry, SIFT-MS, analyses, viz. H_3O^+, NO^+ and $O_2{}^+$, associate with the major components of air and exhaled breath, N_2, O_2 and CO_2. These adduct ions, which include $H_3O^+N_2$, $H_3O^+CO_2$, NO^+CO_2, $O_2{}^+O_2$ and $O_2{}^+CO_2$, are clearly seen when dry air containing 5% CO_2 (typical of that in exhaled breath) is analysed using SIFT-MS. These adduct ions must not be misinterpreted as characteristic product ions of trace gases; if so, serious analytical errors can result. However, when exhaled breath is analysed these adduct ions are partly removed by ligand switching reactions with the abundant water molecules and the problems they represent are alleviated. But the small fractions of the adduct ions that remain in the SIFT-MS spectra, and especially when they are isobaric with genuine characteristic product ion of breath trace gases, can result in erroneous quantifications; such is the case for $H_3O^+N_2$ interfering with breath ethanol analysis and $H_3O^+CO_2$ with breath acetaldehyde analysis. However, these difficulties can be overcome when the isobaric adduct ions are properly recognised and excluded from the analyses; then these two important compounds can be properly quantified in breath. The presence of $O_2{}^+CO_2$ in the product ion spectra interferes with the analysis of CS_2 present at low levels in exhaled breath. It is likely that similar problems will occur as other trace compounds are detected in exhaled breath when consideration will have to be given to the possibility of overlapping between their characteristic product ions and ions produced by hitherto unknown reactions. Similar problems are evident in other systems; for example, $H_3O^+CH_4$ adduct ions are observed in both SIFT-MS analyses of methane rich mixtures like biologically generated waste gases and in model planetary atmospheres.

1. Introduction

The selected ion flow tube technique, principally exploited for the study of the kinetics of ion–molecule reactions that are the chief topic of Professor Herman's research [1], forms the basis of selected ion flow tube mass spectrometry. This technique, now commonly abbreviated as SIFT-MS, has been developed principally for on-line real time quantification of concentrations of trace gases in air, exhaled breath and the headspace above aqueous media such as serum and urine [2–4]. Its utility has been demonstrated in several fields of research [5–7], but it has been mostly applied to breath analysis with a view to assisting clinical diagnosis and therapeutic monitoring [4,8]. Reviews of the principles of SIFT-MS and its application to the various fields, especially breath research, have been presented recently [2,3,9]. Worthy of special mention are the studies of the inter-individual concentration distributions of several trace gas metabolites in exhaled breath for populations of healthy volunteers [8] and the intra-individual concentration distributions of the trace gases in mouth exhaled and nose exhaled breath and in the oral cavity [10,11]. These studies were mostly performed by analysing trace gases in single exhalations of breath directly and on-line to SIFT-MS instruments.

The earliest SIFT-MS instruments, based on the legacy laboratory selected ion flow tube, SIFT [5,12], were the transportable devices *TSIFT Mk.1* and *TSIFT Mk.2* manufactured by Europa Scientific Ltd. UK, which had a detection limit above 10 parts-per-billion (ppb) during the few seconds of a typical breath exhalation period [8,13]. The most recent SIFT-MS instrument, the *Profile 3*, designed by Trans Spectra Ltd UK and manufactured by Instrument Science Ltd UK, has a sensitivity limit of about 1 ppb in a few seconds of integration time and it is this instrument that has been used recently to differentiate between systemically and orally generated

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trace compounds present at levels of a few ppb [11]. An on-going aspect of our research and development effort is directed towards producing smaller and more sensitive SIFT-MS instruments that retain all the unique features of this analytical method, especially that of on-line analyses of single breath exhalations. During this research and development it has been noticed that the ionic reactions on which SIFT-MS analyses are based have components that had not been fully appreciated, principally because these could not be observed in the less sensitive Mk1 and Mk2 SIFT-MS instruments and did not significantly influence analyses at and above the 10 ppb level of detection. These hitherto unimportant reactions involve the slow association of the precursor ions used for SIFT-MS analysis, viz, H_3O^+, NO^+ and $O_2{}^+$, with the major compound gases of ambient air and exhaled breath, viz. N_2, O_2, and CO_2. Such three-body association reactions are facilitated by the helium atoms, He, that constitute the carrier gas in the SIFT-MS flow tube reactor. The essential point, as will be described thoroughly below, is that weakly bound adduct ions of the kind $H_3O^+N_2$ and NO^+CO_2 form at the high number densities of these neutral gases (N_2 and CO_2 that constitute the large fraction of air/breath samples) and these adduct ions are seen in the product ion spectra that are the formal basis of SIFT-MS analyses. We have also very recently seen, to our surprise, the formation of the adduct ion species $H_3O^+CH_4$ in methane-rich samples, including biologically generated waste gases and model planetary atmospheres; pilot data from the analyses of some such samples are given in this paper. Of course, if such adduct ions are recognised and the kinetics of their formation established then, in principle, their presence in SIFT-MS spectra can be accounted for thus avoiding erroneous diagnoses and analyses. However, the situation is potentially even more complicated in that these weakly bound adduct ions can react with other species, including the trace gases, M, that are present in the samples to be analysed (notably by ligand switching; see Reactions (4) and (5) later) to produce a range of more strongly bound adduct ions like H_3O^+M, NO^+M and $O_2{}^+M$. In effect, the weakly bound adduct ions can act as intermediates for the production of the latter, more stable adduct ions.

Similar sequences of association reactions have been well recognised during the period of development of the SIFT-MS analytical method, especially when analysing humid breath (water vapour present at about 6% by volume). Thus, the adduct (hydrated) ions $H_3O^+(H_2O)_{1,2,3}$, $NO^+(H_2O)_{1,2}$ and $O_2{}^+(H_2O)_{1,2}$ appear as integral parts of the spectra formed by the three precursor ions species; they play an important part in the overall ion chemistry involved in SIFT-MS trace gas analysis and must be accounted for if accurate analyses are to be obtained [14]. That these hydrated ions so readily form and are obvious in SIFT-MS spectra is because of the high humidity of breath samples and because the binding energies of water molecules to the H_3O^+, NO^+ and $O_2{}^+$ precursor ions are relatively large; thus the adduct ions are quite stable against dissociation at the temperature of the helium carrier gas (usually close to 300 K) in which they are formed and exist. Although the partial pressures of N_2 and O_2 are relatively high in air samples, and additionally CO_2 in breath samples, the binding energies of these compound molecules with the SIFT-MS precursor ions are relatively low, so the formation rates of the adduct ions, e.g., $H_3O^+N_2$, NO^+CO_2, $O_2{}^+CO_2$, are expected to be slow and they might well be unstable against dissociation in the helium carrier gas. Indeed, it is then likely that they might be in equilibrium with their reactants in the helium carrier gas. Nevertheless, as mentioned above, they are surely very reactive with the water molecules that are inevitably present in ambient air and exhaled breath. We will refer to these reactions later in this paper.

It is now essential to understand this collateral ion chemistry involving the major neutral species that are present at very high concentrations in air/breath samples (N_2, O_2, CO_2) if analyses are to be carried out at sub-ppb levels by SIFT-MS. Thus, in this paper, we consider the formation of some of the weakly bound adduct ions referred to above and assess their possible effects on SIFT-MS analyses.

2. Basic operation of SIFT-MS and the primary ion chemistry

The SIFT-MS technique has been described in previous papers [2,4] so only a very brief description is required here, but additionally to include notes on the essential ion chemistry on which SIFT-MS relies in order to set the scene for the important issue involved in the new work that is the focus of this paper. The precursor ions H_3O^+, NO^+ and $O_2{}^+$ are formed in a microwave discharge source and are selected according to their mass-to-charge ratio, m/z, by a mass filter and injected into flowing helium carrier gas where they are convected as a thermalised swarm along a flow tube. Sample gas (air, breath, liquid headspace that are often very humid) is introduced at a known flow rate into the helium and the precursor ions and the product ions of their reactions with the trace gases in the sample are detected and counted by a downstream analytical mass spectrometer system. For the purposes of the special focus of this paper it is important to emphasize that the reactions of the precursor ions with trace gases in the samples to be analysed (usually volatile organic compounds) are almost always rapid, the rate coefficients being at or very close to the collisional limiting values, k_c [15,16]. Thus, H_3O^+ reacts with most compounds, M, via rapid proton transfer producing MH^+ ions, NO^+ undergoes rapid charge transfer, hydride ion transfer or adduct formation producing M^+, $(M–H)^+$ and NO^+M ions respectively, and most $O_2{}^+$ reactions proceed via charge transfer producing nascent excited M^{+*} ions that often fragment. Numerous reactions between these precursor ions and a wide variety of organic compounds have been studies that illustrate the processes involved [2,17]. By identifying the characteristic product ions of the trace gases in the sample and knowing the rate coefficients for the reaction that produce them, the concentrations (levels) of the trace compounds in the sample are obtained [14]. Should the rate coefficient for a particular reaction be unknown it can be determined by introducing the pure compound into the helium carrier gas at a known flow rate that is sufficiently high to reduce the precursor ion count rates at the downstream mass spectrometer by about an order-of-magnitude or more, as described in previous papers reviewed in [2]. In this way, the rate coefficients and the product ions for the reactions of H_3O^+, NO^+ and $O_2{}^+$ have been determined with many types of compounds [2,18] from which a large kinetics library has been built in support of SIFT-MS analyses [14]. Unfortunately, this procedure is not feasible for reactions that are very slow, such as the reactions that form the adduct ions that are the focus of the present paper, because the flow rates of the gases into the helium carrier gas would need to be too high to significantly reduce the count rates of the precursor ions and then the reactive gas becomes a major fraction of the carrier gas, which seriously complicates the flow dynamics. Fortunately, many of these slow reactions that form the adduct ion we are concerned with have been measured previously using more suitable techniques [19–25].

3. Adduct ion formation involving the major components of air/breath samples

The major components of air/breath samples are N_2, at about 80% by volume in air and breath, O_2, at about 20% (air) and 15% (exhaled breath), CO_2, at about 5% in exhaled breath and water vapour, at typically 1.5–2% in ambient air and about 6% in exhaled breath. Other species are present at much lower levels, including argon (about 1% in air), which need not be considered here. However, it is necessary to note that when analysing the composition of some biologically generated gaseous waste, gases other than the above might be present at very high levels, which might produce unexpected ions in SIFT-MS spectra. An example is methane, CH_4, which appears at very high levels in gases produced from sewage treatment plants, municipal landfills and farm waste.

3.1. *Precursor ion/water molecule reactions: adduct ion formation*

As a prelude to the discussion of the slow association reactions of N_2, $O_2^{+\bullet}$ and CO_2 with H_3O^+, NO^+ and $O_2^{+\bullet}$, we discuss the more rapid reactions of water molecules with these ions. There is a considerable amount of kinetic data on these reactions [19,26,20]. For the ground electronic states of these ions there are no exothermic two-body bimolecular reactions that are energetically possible and so they all proceed via three-body termolecular association to produce adduct or cluster ions. This ion chemistry is important in the terrestrial ionosphere and thus these processes were researched and understood in great detail in the early 1970s [21,22]. The initial steps, in what are complex reaction sequences, are exemplified by the following reactions:

$$H_3O^+ + H_2O + He \rightarrow H_3O^+H_2O + He \quad (1)$$

$$NO^+ + H_2O + He \rightarrow NO^+H_2O + He \quad (2)$$

$$O_2^{+\bullet} + H_2O + He \leftrightarrow O_2^{+\bullet}H_2O + He \quad (3)$$

In SIFT-MS, these reactions are mediated by the presence of the abundant atoms of the helium carrier (buffer) gas (typically at a pressure of about 1 Torr in SIFT-MS instruments, equivalent to a helium atom number density [He] of $3 \times 10^{16}\,cm^{-3}$). Collisions of the nascent excited adduct ions, e.g., $(H_3O^+H_2O)^*$, with helium atoms stabilise them against dissociation back to the reactants. The termolecular rate coefficients, k_3, for Reactions (1)–(3) have been measured under thermalised conditions at 300 K (that pertain to the conditions in the SIFT-MS reaction region) to be $6.65 \times 10^{-28}\,cm^6\,s^{-1}$, $3.2 \times 10^{-29}\,cm^6\,s^{-1}$ and $8.7 \times 10^{-29}\,cm^6\,s^{-1}$ respectively [23–25]. The binding energies of the ion/molecule adducts are H_3O^+/H_2O, 136 ± 9 kJ/mol [27], NO^+/H_2O, 82 ± 15 kJ/mol [22], $O_2^{+\bullet}/H_2O$ ~71 kJ/mol [21]). Under typical conditions of SIFT-MS, a helium pressure of 1 Torr at 300 K, these k_3 values translate to effective bimolecular rate coefficients, k_{2eff} (=k_3[He]) of $2.1 \times 10^{-11}\,cm^3\,s^{-1}$, $1 \times 10^{-12}\,cm^3\,s^{-1}$ and $2.8 \times 10^{-12}\,cm^3\,s^{-1}$ respectively These k_{2eff} values are very low compared to the collisional rate coefficients, k_c, that describe almost all of the bimolecular reactions of the precursor ions with trace gases that are involved in SIFT-MS analyses; these are within the range ($1 \times 10^{-9}\,cm^3\,s^{-1}$ to $5 \times 10^{-9}\,cm^3\,s^{-1}$). Nevertheless, the formation rates of the hydrated ions via Reactions (1)–(3) are fast enough to produce significant fractions of the adduct ions, since the water molecule number density in the helium carrier gas is relatively high when analysing humid samples, including exhaled breath samples, when it is about $10^{14}\,cm^{-3}$. Sample SIFT-MS spectra showing the presence of these adduct (hydrated) ion are presented later, which also show that higher-order hydrated ions are also formed, viz. $H_3O^+(H_2O)_{2,3,4}$, $NO^+(H_2O)_{2,3}$ and $O_2^{+\bullet}(H_2O)_2$. Given the relative magnitudes of the rate coefficients for Reactions (1)–(3) it is no surprise that the hydrates of H_3O^+ are more abundant than those of NO^+. The hydrates of $O_2^{+\bullet}$ are even less abundant, as the later SIFT-MS spectra reveal, because they react with water molecules by the fast bimolecular Reaction (14) that is discussed later in Section 3.2.3 and in [21]. In SIFT-MS, these hydrated ions can undergo ligand switching reactions with trace gas molecules, M, especially polar molecules, to produce ions of the type MH^+H_2O and NO^+M [17]:

$$H_3O^+H_2O + M \rightarrow H_3O^+M\,(\text{or } MH^+H_2O) + H_2O \quad (4)$$

$$NO^+H_2O + M \rightarrow NO^+M + H_2O \quad (5)$$

These adduct ions must be accounted for if accurate SIFT-MS analyses are to be obtained [14]. Ligand switching reactions are also very important in removing more weakly bound adduct ions, such as $H_3O^+N_2$ and $O_2^+CO_2$, etc. as indicated below.

3.2. *Precursor ion/N_2, O_2, CO_2 reactions: adduct ion formation*

Combining the three precursor ions H_3O^+, NO^+ and O_2^+ with the three abundant neutral molecules requires that nine possible adduct ions be considered. Guidance on which are important in SIFT-MS is obtained by inspection of the spectra obtained for each precursor ion species as dry neutral gases of appropriate composition are introduced into the helium carrier gas at flow rates that mimic typical sample flow rates used in SIFT-MS. It is essential that the neutral gases be as dry as possible since, as already mentioned and discussed later, the weakly bound adduct ions react rapidly with water molecules. However, the latter is an advantage in practical analysis of breath, because the weakly bound adducts can be rapidly removed from the carrier gas as they are formed and thus they will have a diminishing influence on the trace gas analyses. We now consider the adduct reactions of each precursor ion in turn.

3.2.1. *H_3O^+ precursor ions*

A SIFT-MS analytical spectrum obtained as a mixture of dry air containing about 5% by volume of CO_2 is introduced into the helium carrier gas is shown in Fig. 1a. In addition to the expected $H_3O^+(H_2O)_{1,2,3,4}$ hydrated ions at *m*/*z* 37, 55, 73, 91 and their ^2H, ^{17}O and ^{18}O isotopologues, the adduct ions of H_3O^+ with N_2 (*m*/*z* 47) and with CO_2 (*m*/*z* 63) are obvious, but there is no evidence for $H_3O^+O_2$ (*m*/*z* 51) ions. This implies that the binding energies of the last ion is too small for it to form and remain stable at 300 K, whereas the first two ions are more strongly bound and are clearly stable in the dry helium carrier gas. They are formed in the three-body association reactions:

$$H_3O^+ + N_2 + He \rightarrow H_3O^+N_2 + He \quad (6)$$

$$H_3O^+ + CO_2 + He \rightarrow H_3O^+CO_2 + He \quad (7)$$

The other minor ions are mostly due to impurities in the air/CO_2 sample mixture, although some are readily recognisable such as $H_4O_2^{+\bullet}$ (*m*/*z* 36), $O_2^{+\bullet}H_2O$ (*m*/*z* 50) and $CO_2^{+\bullet}CO_2$ (*m*/*z* 88), the first of which will be discussed later when discussing the $O_2^{+\bullet}$ adduct reactions. The $O_2^+H_2O$ ions are formed from the (always present) impurity O_2^+ ions via the association Reaction (3). It is not certain how the $CO_2^+CO_2$ ions form, but they probably originate from the relatively abundant $H_3O^+CO_2$ adduct ions by, as yet, undefined ion chemistry.

The appearance of the $H_3O^+N_2$ and $H_3O^+CO_2$ adduct ions is of particular significance in SIFT-MS, because the former is isobaric with protonated ethanol, $C_2H_5OH_2^+$, and the latter is isobaric with monohydrated protonated acetaldehyde, $CH_3CHOH^+H_2O$. Both ethanol and acetaldehyde are important in breath research [2,4] and biology [28] and, as such, it is desirable to be able to accurately quantify these compounds using SIFT-MS, so this ion overlap presents a problem. Fortunately, the situation is partially resolved when analysing humid air/breath samples, because the adduct ions react very rapidly with water, thus:

$$H_3O^+N_2 + H_2O \rightarrow H_3O^+H_2O + N_2 \quad (8)$$

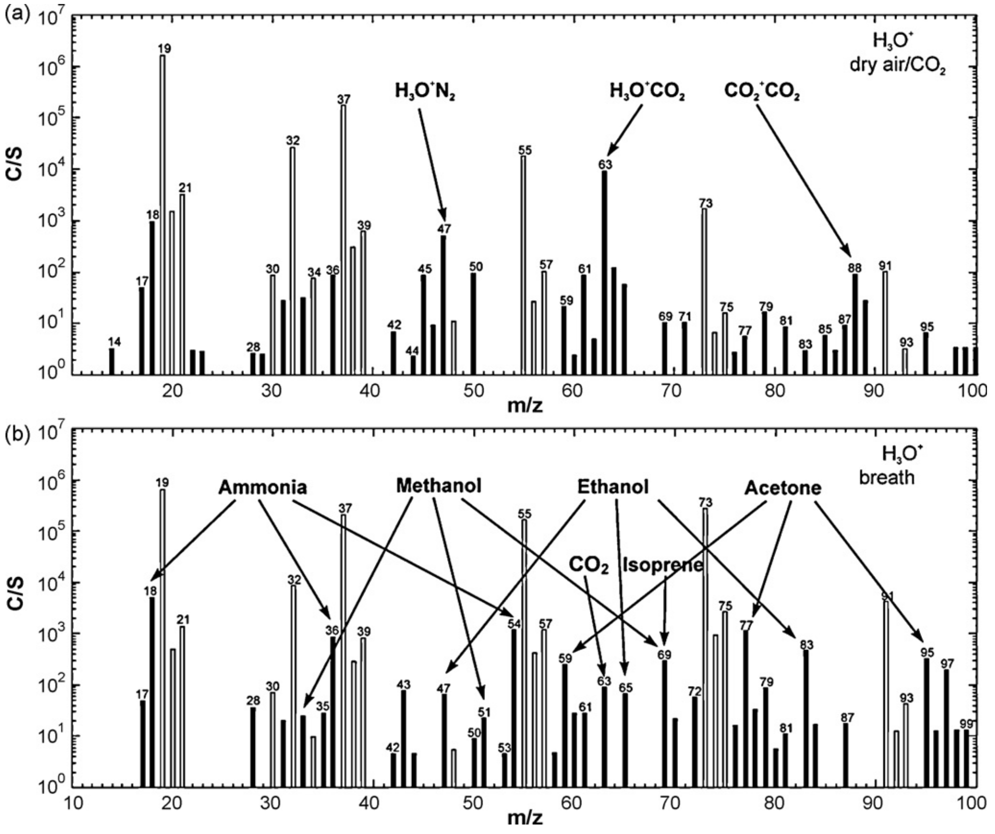

Fig. 1. (a) A SIFT-MS spectrum obtained using H_3O^+ ions for the analysis of dry cylinder air containing about 5% of CO_2. Note the clear peaks adduct ion peaks of $H_3O^+N_2$ and $H_3O^+CO_2$ at mass-to-charge ratio, *m*/*z*, 47 and 63 and that at *m*/*z* 88, which is $CO_2{}^+CO_2$. The open peaks are H_3O^+ and its hydrates, $H_3O^+(H_2O)_{1,2,3,4}$, and their ^2H, ^{17}O and ^{18}O isotopologues. (b) The analogous spectrum obtained for the analysis of exhaled breath. Notice the great reduction in the peak heights at *m*/*z* 47 and 63 due to the reactions of the adduct ions with H_2O molecules and the great increase in the heights of the H_3O^+ hydrate ions. Also, note the appearance of the characteristic ions of the common breath trace gases, as indicated.

$$H_3O^+CO_2 + H_2O \rightarrow H_3O^+H_2O + CO_2 \tag{9}$$

These ligand switching reactions are exothermic by virtue of the fact that both N_2 and CO_2 are much more weakly bonded to H_3O^+ than is H_2O. Reactions such as (8) and (9) are well known to proceed at or close to the collisional rate [17,26,20] and so in the presence of water molecules the weakly bound ions will be mostly destroyed. Even the spectrum obtained using the ostensibly dry air/CO_2 mixture (Fig. 1a) includes an appreciable *m*/*z* 37 signal, $H_3O^+H_2O$, which shows the speed of these switching reactions that catalyse the production of the latter H_3O^+ hydrate ion. At the humidity of ambient air, which is typically 1–2%, the number density of H_2O molecules in the helium (typically $3 \times 10^{13}\,cm^{-3}$) coupled with a rate coefficient of $2 \times 10^{-9}\,cm^3\,s^{-1}$ for the switching Reactions (8) and (9) ensures a rapid destruction of the adduct ions, i.e., in decay times of about 2×10^{-5} s, as compared to the available reaction time in the *Profile 3* SIFT-MS instruments of typically 4×10^{-4} s. So, given the high number density of water molecules in humid samples of ambient air/breath (typically 6% by volume) the lifetimes of the N_2 and CO_2 adduct ions are very short in the SIFT-MS flow tube. That this is so is seen in the spectrum in Fig. 1b, which is the spectrum obtained when exhaled breath (also containing about 5% CO_2 but with about 6% water vapour) is introduced into the helium carrier gas. Now the signal levels of the adduct ions present at *m*/*z* values of 47 and 63 are much smaller, but they are still seen in the spectrum at a level of about 100 c/s. We understand this to mean, in part, that Reactions (6) and (7) are in forward/reverse equilibrium at the high levels of N_2 and CO_2 present in the sample gas mixture and, whereas the equilibrium is well to the right, there may remain small fractions of both $H_3O^+N_2$ and $H_3O^+CO_2$ in the carrier gas. These small fractions could interfere with the analyses of ethanol and acetaldehyde in exhaled breath, especially acetaldehyde that is present only at levels of only a few ppb [8]. However, part of the *m*/*z* 47 ions seen in Fig. 1b is indeed due to protonated ethanol, a conclusion supported by the presence of its hydrates $C_2H_5OH_2{}^+(H_2O)_{1,2}$, as indicated in Fig. 1b (remembering that $H_3O^+N_2$ will not form a second hydrate but rather react with water molecules to form $H_3O^+H_2O$). Similarly, the large part of the *m*/*z* 63 signal is due to $H_3O^+CO_2$ and only a small fraction is due to breath acetaldehyde. To account for the interferences of these adduct ions, we have developed methods that avoid the use of *m*/*z* 47 for ethanol analysis (by using only the doubly hydrated ion $C_2H_5OH_2{}^+(H_2O)$ at *m*/*z* 83) and *m*/*z* 63 for acetaldehyde (by using only the CH_3CHOH^+ and $CH_3CHOH^+(H_2O)_2$ ions at *m*/*z* 45 and 81 respectively) and now the analyses of these compounds in breath can be carried out to reasonable accuracy. This work is reported in detail in a recent paper [29]. It is interesting to note that the signal level at *m*/*z* 63 seen when analysing exhaled breath can, in principal, be used to quantify CO_2 in exhaled breath and in other air samples, especially when acetaldehyde and other molecules with molecular weights of 62 (e.g., dimethylsulphide, $(CH_3)_2S$) that are protonated by H_3O^+ ions are absent. When analysing exhaled breath using the current *Profile 3* instruments, the *m*/*z* 63 signal is comprised of about 90% due to $H_3O^+CO_2$ ions, the remaining percentage being due to the presence of acetaldehyde/dimethylsulphide. These preliminary results provide sufficient stimulus for further investigations into the potential use of SIFT-MS for CO_2 quantification in air/breath samples.

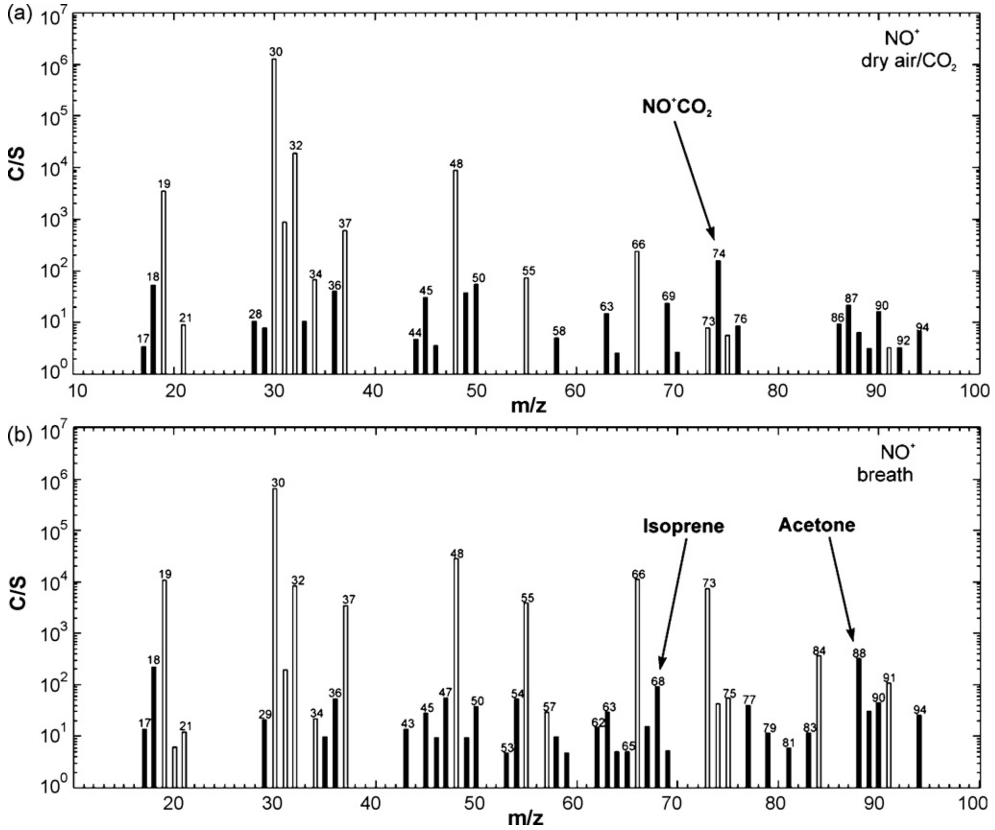

Fig. 2. (a) A SIFT-MS spectrum obtained using NO^+ ions for the analysis of dry cylinder air containing about 5% of CO_2. Note the clear peaks adduct ion peak of NO^+CO_2 at a mass-to-charge ratio, *m*/*z*, of 74. The open peaks are NO^+ and its hydrates, $NO^+(H_2O)_{1,2}$. (b) The analogous spectrum obtained for the analysis of exhaled breath. Notice the great reduction in the peak height at *m*/*z* 74 due to the reactions of the adduct ion with H_2O molecules and the great increase in the heights of the $NO^+(H_2O)_{1,2}$ and the appearance of the third hydrate $NO^+(H_2O)_3$ at *m*/*z* 84, and the increase in the H_3O^+ hydrate ions. Also, note the appearance of the characteristic ions of the common breath trace gases, as indicated.

3.2.2. NO^+ precursor ions

The spectrum obtained using NO^+ ions when the dry air/CO_2 mixture is introduced into the helium carrier gas is shown in Fig. 2a. As expected, the $NO^+(H_2O)_{1,2}$ hydrated ions appear at *m*/*z* 48 and 66 at low levels, but there is no indication of the presence of the adduct ions NO^+N_2 (*m*/*z* 58) and NO^+O_2 (*m*/*z* 62). This is because the binding energies of these adduct ions are very small (22 kJ/mol for $NO^+–N_2$ and 16 kJ/mol for $NO^+–O_2$ [30]); consequently, the rate coefficients of the $NO^+/N_2/He$ and $NO^+/O_2/He$ termolecular reactions that can form them in the SIFT-MS reactor at 300 K are very small at $<5 \times 10^{-33}\,cm^6\,s^{-1}$ and $<6 \times 10^{-34}\,cm^6\,s^{-1}$ respectively [31]. As such, these ions cannot exist in significant fractions in the helium carrier gas at 300 K. However, there is clearly an ion present at *m*/*z* 74 in the spectrum in Fig. 2a, which is the NO^+CO_2 adduct, a known stable ion that is involved in atmospheric ion chemistry [32]. It is formed by the association reaction:

$$NO^+ + CO_2 + He \rightarrow NO^+CO_2 + He \qquad (10)$$

The rate coefficient for this reaction has been measured to be $4.5 \times 10^{-30}\,cm^6\,s^{-1}$ at 300 K [31], which is several times greater than those corresponding N_2 and O_2 reactions referred to above. However, it is also expected that the NO^+CO_2 adduct ion will undergo ligand switching with H_2O molecules (analogous to Reactions (8) and (9)) and will thus efficiently be lost when analysing humid samples. This should be evident when analysing exhaled breath; a related spectrum is shown in Fig. 2b where the much smaller signal at *m*/*z* 74 is entirely due to the ^2H and ^{17}O isotopologues of the $H_3O^+(H_2O)_3$ ion at *m*/*z* 73. Fortunately, the precise signal level ratios the H_3O^+ hydrates ions at *m*/*z* values of 73, 74 and 75 are well known when they are derived from water vapour as a result of our extensive work and development of flowing afterglow mass spectrometry, FA-MS, used for the determination of the deuterium content of water vapour [33]. Thus, a check can be made for any contribution of NO^+CO_2 to the ions at *m*/*z* 74 in SIFT-MS spectra when analysing breath and it can be shown that such a contribution is negligible. To date, we have not discovered any other trace gas compounds to exist in exhaled breath that produce product ions at *m*/*z* 74 when using NO^+ precursor ions. If such was discovered the overlap with the inevitable $H_3O^+(H_2O)_3$ ions isotopologues would make its analysis challenging.

3.2.3. $O_2^{+\bullet}$ precursor ions

This radical cation, $O_2^{+\bullet}$, forms adducts with all three of the neutral compounds under consideration here via the reactions:

$$O_2^{+\bullet} + N_2 + He \rightarrow O_2^{+\bullet}N_2 + He \qquad (11)$$

$$O_2^{+\bullet} + O_2 + He \rightarrow O_2^{+\bullet}O_2 + He \qquad (12)$$

$$O_2^{+\bullet} + CO_2 + He \rightarrow O_2^{+\bullet}CO_2 + He \qquad (13)$$

Thus, in the spectrum shown in Fig. 3a produced when the dry air/CO_2 mixture is introduced into the helium carrier gas using $O_2^{+\bullet}$ precursor ions, adduct ions appear at *m*/*z* values of 60 ($O_2^{+\bullet}N_2$), 64 ($O_2^{+\bullet}O_2$) and 76 ($O_2^{+\bullet}CO_2$) as formed in these termolecular reactions. In addition, the ion at *m*/*z* 50 is very obvious, which is $O_2^+H_2O$ formed due to the presence of traces of water vapour by Reaction (3) given previously, and an ion at *m*/*z* 36. Of these ions, the appearance of the last is perhaps most surprising, so its binding energy must be appreciable. This rules out $O_2^{+\bullet}He$, which must have a very low

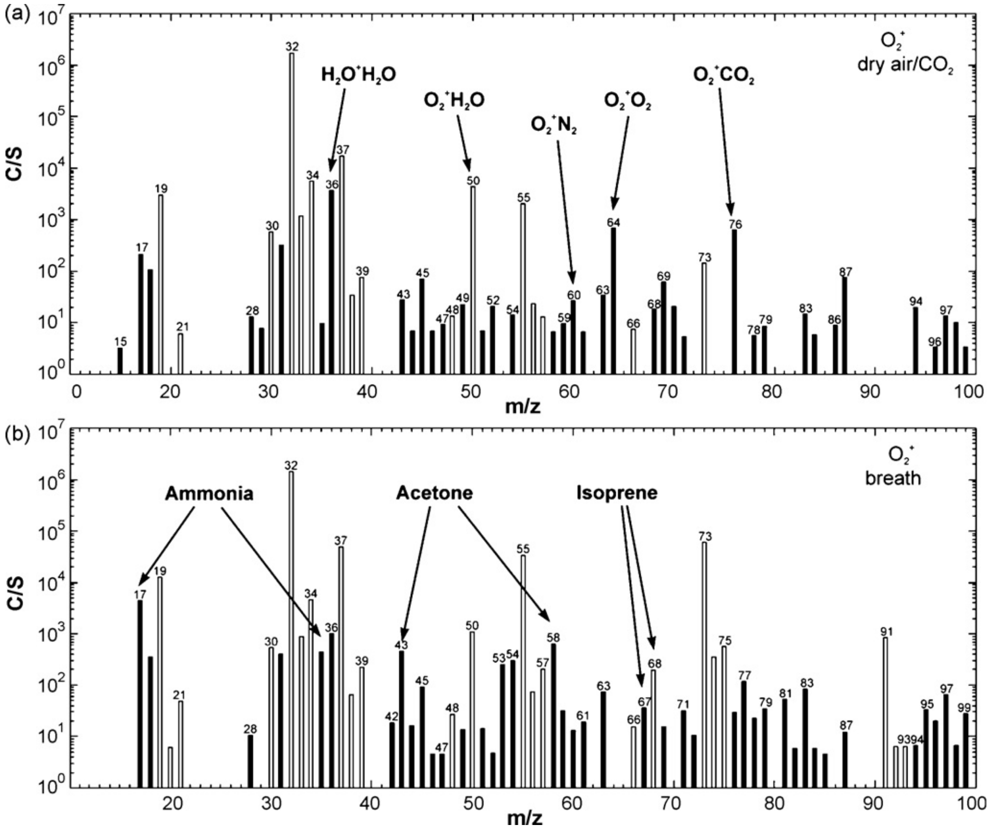

Fig. 3. (a) A SIFT-MS spectrum obtained using O_2^+ ions for the analysis of dry cylinder air containing about 5% of CO_2. Note the clear peaks adduct ion peaks of $H_2O^+H_2O$, $O_2^+H_2O$, $O_2^+O_2$ and $O_2^+CO_2$ at mass-to-charge ratios, *m*/*z*, of 36, 50, 64 and 76. The open peaks are O_2^+ and the $H_3O^+(H_2O)_{0,1,2,3,4}$, ions. (b) The analogous spectrum obtained for the analysis of exhaled breath. Notice the great reduction in the peak height at *m*/*z* 36 and 50 and the absence of those at 64 and 76 due to the reactions of these adduct ion with H_2O molecules. Also, note the appearance of the characteristic ions of the common breath trace gases, as indicated.

binding energy and, significantly, it has only been seen in ionised gases at very low temperatures [34]. This leaves as the only candidate $H_2O^{+\bullet}H_2O$; we discuss the formation of this unusual ion below. Of the other three adduct ions, the $O_2^+N_2$ ion is at a relatively low level considering that the N_2 concentration is some 4 times greater than that of O_2 and about 20 times greater than that of CO_2. This is surely because the binding energy of N_2 to $O_2^{+\bullet}$ is very small [27] and the rate coefficient for Reaction (11) is correspondingly small. It is known that the analogous $O_2^{+\bullet}/N_2/N_2$ association reaction has a termolecular rate coefficient of 8×10^{-31} cm^6 s^{-1} at 300 K [19] and surely the He mediated reaction will be even slower than this. The binding energies of $O_2^{+\bullet}O_2$ and $O_2^{+\bullet}CO_2$ ion species have both been evaluated as 41 kJ/mol [27,35,36]. Strictly speaking, these two ion species should not be viewed as simple adducts, because they do have recognised covalent bounding [35,36], but they do behave as adducts in the sense that they readily undergo switching reactions with H_2O molecules of the kind indicated by Reactions (8) and (9). Thus, when analysing exhaled breath, the resultant spectrum in Fig. 3b shows no peak at *m*/*z* 64, indicating that the $O_2^{+\bullet}O_2$ ions are absent. The peak at *m*/*z* 74 is consistent with the minor isotopic variants of the abundant $H_3O^+(H_2O)_3$ ions.

The signal at *m*/*z* 36, although much smaller in the presence of the H_2O molecules, appears to persist at a low level and this needs further investigation. It was clear in these experiments that the signals at *m*/*z* 36 and 50, $H_4O_2^{+\bullet}$ and $O_2^{+\bullet}H_2O$ ions, both increased in sympathy as the water level in the helium was increased. Further to this, the $H_4O_2^{+\bullet}/O_2^{+\bullet}H_2O$ signal ratio remained sensibly constant at a value of close to 1.3 as the water molecule number density in the carrier gas increases. We expect the $O_2^{+\bullet}H_2O$ signal level to increase with increasing water vapour number density due to the increasing rate of Reaction (3), but why should the $H_4O_2^{+\bullet}$ increase? This can be explained by the production of the $H_4O_2^{+\bullet}$ ions via the switching reaction first described in [21]:

$$O_2^{+\bullet}H_2O + H_2O \rightarrow H_4O_2^{+\bullet} + O_2 \tag{14}$$

Reaction (14) proceeds at the gas kinetic rate, the rate coefficient being 1.9×10^{-9} cm^3 s^{-1}. In the original paper [21] the structure of this product is written as $H_3O^+{\cdot}OH^\bullet$ and it is equivalent to $H_2O^{+\bullet}H_2O$ with a bond energy of 150 kJ/mol [27]. This ion species has also been seen to form in the reactions of Kr^+H_2O and Xe^+H_2O ions with H_2O [37]. Reaction (14) is exothermic, but as described in [21], the $H_4O_2^+$ product ions immediately react further with H_2O in another gas kinetic binary reaction:

$$H_4O_2^{+\bullet} + H_2O \rightarrow H_3O^+H_2O + OH^\bullet \tag{15}$$

The rate coefficient for this reaction has been measured as 3×10^{-9} cm^3 s^{-1} and its exothermicity determined to be 90 kJ/mol. Thus, the formation rate of the $H_2O^{+\bullet}H_2O$ ion via Reaction (14) is balanced by its loss by Reaction (15) and their signal ratio does not change with H_2O concentration [21] as indicated by our SIFT-MS observations.

Note, the increased signal levels of the $H_3O^+(H_2O)_{1,2,3}$ ions in the breath spectrum in Fig. 3b. It is known from numerous studies of ions in the upper terrestrial atmosphere that these hydrated hydronium ions are formed in a sequence of reactions involving the formation of the weakly bound adduct ions described in this paper followed by reactions such as (14) and (15) and this is surely happening in the SIFT-MS carrier gas when humid breath is being analysed.

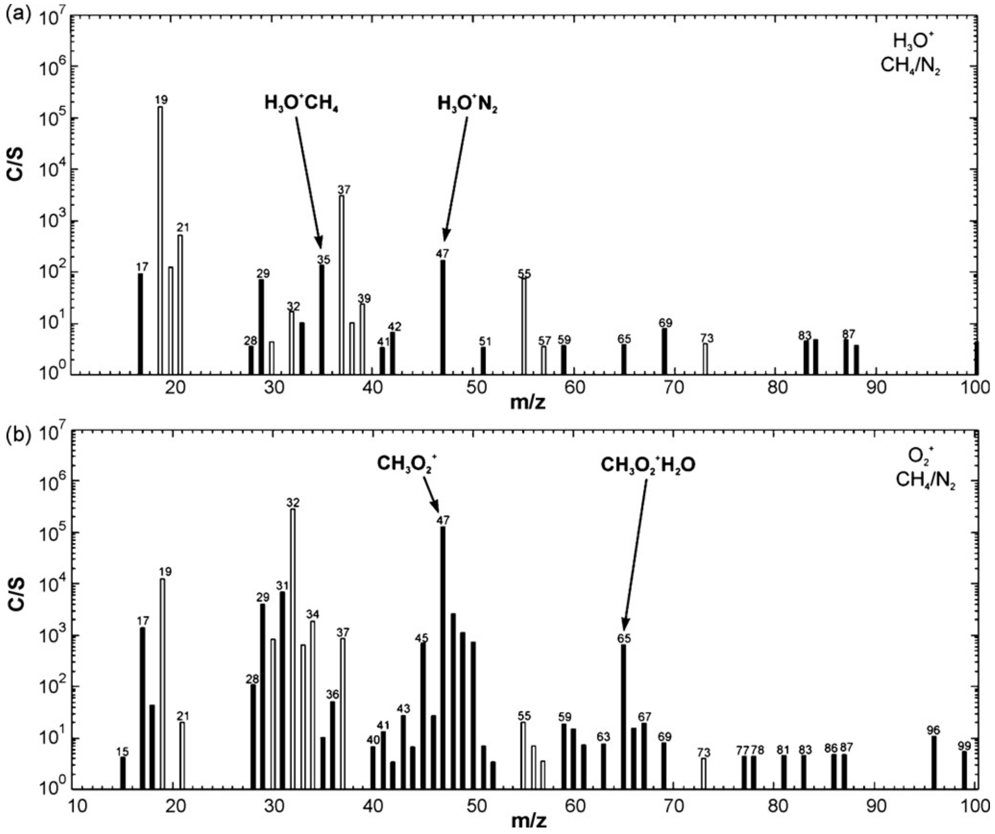

Fig. 4. (a) A SIFT-MS spectrum obtained using H_3O^+ precursor ions as a 50%/50% mixture of methane and nitrogen with a trace of water vapour is introduced into the helium carrier gas. Note, in particular, the appearance of the adduct ions at *m*/*z* values of 35 and 47. (b) The corresponding spectrum observed using O_2^+ precursor ions to analyse the same mixture and the large product ion at *m*/*z* 47 and its weaker hydrate at *m*/*z* 65.

4. Reactions of methane, CH_4

As previously mentioned, it is to be expected that association might occur between the SIFT-MS precursor ions and other normally "inert" neutral gases when they are present at high concentrations beyond the trace levels normally explored using SIFT-MS. A case in point is CH_4, which often appears at percentage levels in the bio-gas generated from animal waste, sewage and municipal waste. To investigate the use of SIFT-MS to analyse methane, a mixture of 50%/50% methane and nitrogen was introduced into the carrier gas and the spectrum obtained using H_3O^+ precursor ions is shown in Fig. 4a. The product ion at *m*/*z* 35 would normally be interpreted as protonated hydrogen sulphide, H_3S^+, as expected for proton transfer from H_3O^+ to H_2S [2], but the peak height correlates with the flow rate of the CH_4/N_2 mixture and so this *m*/*z* 35 ion is attributed to the adduct ion $H_3O^+CH_4$ as formed in the reaction:

$$H_3O^+ + CH_4 + He \rightarrow H_3O^+CH_4 + He \tag{16}$$

However, the relatively small level of this product ion peak coupled with the relatively large flow of methane indicates that this reaction cannot be used to analyse methane in mixtures even when present at very high concentrations. Note in the spectrum in Fig. 4a that the peak height of the *m*/*z* 35 and 47 product ions are comparable, indicating that the termolecular rate coefficient for Reaction (16) is similar to that for the slow Reaction (6) that forms the adduct ion $H_3O^+N_2$, as discussed in Section 3.2.1.

Much more promising for practical quantification of methane using SIFT-MS is to use O_2^+ precursor ions, as explored by McEwan and coworkers [7]. The spectrum obtained when the CH_4/N_2 mixture is flowed into the helium carrier gas (at the same rate as used to obtain the spectrum shown in Fig. 4a) is shown in Fig. 4b where it can be seen that a dominant peak is seen at *m*/*z* 47. This results from the following reaction:

$$O_2^{+\bullet} + CH_4 \rightarrow CH_3O_2^+ + H^\bullet \tag{17}$$

This bimolecular Reaction (17) has received considerable attention over many years and is known to be very slow and inefficient, the measured rate coefficients being ($5 \times 10^{-12}\,cm^3\,s^{-1}$ to $6 \times 10^{-12}\,cm^3\,s^{-1}$ at 300 K [19] compared to the collisional rate coefficient of $2 \times 10^{-9}\,cm^3\,s^{-1}$. Nevertheless, at high concentrations of CH_4 in the sample to be analysed then the product ion $CH_3O_2^+$ can be used to quantify CH_4.

5. Concluding remarks

Hitherto in the development and use of SIFT-MS it has been possible to ignore the influence of the major gases present in air (N_2, O_2) and exhaled breath (additionally CO_2) when analysing them for trace gases, because previously the sensitivity of the technique limited measurements of the said trace gases to about 10 ppb in times of a few seconds. Now, with the great improvements in the sensitivity of current SIFT-MS instruments, which allow measurements at the ppb level in times of the few seconds typical of a single breath exhalation, the influence of the major gases has become apparent, and it is seen that reactions forming the adduct ions that comprise the reagent precursor ions and the major gas molecules, for example, $H_3O^+N_2$ and $O_2^{+\bullet}O_2$, can be troublesome, especially in analysing the trace gases present in exhaled breath. If the presence of these ions is not recognised, they can be improperly assigned to compounds that are not present (e.g., $H_3O^+N_2$ as protonated ethanol) and result in falsely high analyses of trace compounds, especially when the adduct ions are isobaric with the characteristic product ions of a particular trace gas (e.g., $H_3O^+CO_2$ as the monohydrate of protonated acetaldehyde). The purpose of this paper is to show how these adduct ions can be identified by observing the product ion spectra that form when a dry air containing 5% CO_2 (the typical fractional content of exhaled breath) is introduced into the SIFT-MS carrier gas. Under these conditions the adduct ions are seen at appreciable signal levels that can result in serious analytical errors if not accounted for. However, in humid exhaled breath analyses the signal levels of the adduct ions are greatly reduced, because they rapidly react with water molecules in ligand switching reactions, generating the ions $H_3O^+H_2O$, NO^+H_2O and $O_2^{+\bullet}H_2O$, which are always present in SIFT-MS spectra, the presence of which are routinely accounted for in the analysis of trace gases [14]. Nevertheless, some of these interfering adduct ions are not totally lost by reactions with water molecules and they can partially remain when analysing breath samples. We have shown that these interferences can be accounted for in some cases by excluding from the analysis the particular m/z ions at which ion overlap of these adduct ions occurs with genuine characteristic product ions. This has been successfully achieved for the analyses of ethanol and acetaldehyde in exhaled breath [29] and doubtlessly similar procedures will be required as other trace gases are identified in exhaled breath. The occurrence of the $O_2^{+\bullet}CO_2$ adduct ion at m/z 76 masks the CS_2^+ ion, which unfortunately means that CS_2 cannot be quantified in exhaled breath at levels <50 ppb [38]. The essential point that emerges from these studies is that to identify and quantify trace gases at levels as low as ppb and below in ion chemical reactors requires very careful consideration of all possible ion chemical routes to the assumed characteristic product ions; otherwise serious errors in analysis are likely.

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