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Concurrent use of H_3O^+, NO^+, and O_2^+ precursor ions for the detection and quantification of diverse trace gases in the presence of air and breath by selected ion-flow tube mass spectrometry

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Abstract

Selected ion-flow tube mass spectrometry, SIFT-MS, relies on chemical ionization of trace gases in air and breath samples using precursor ions that can be rapidly changed to allow the analysis of transient or limited-volume samples. The precursor ion species of choice are H_3O^+, NO^+ and O_2^+ because they do not react with the major components of air. In this article, we present the results of a study designed to investigate if consistent quantification of chemically different compounds can be realized using these three precursor ion species in the presence of humid air and breath. The neutral compounds included in the study are ammonia, dimethylamine, acetone, benzene, isoprene, ethanol, and 1-propanol. These were chosen primarily because the reactions of these compounds with the three precursor ions are representative of the diverse ion chemistry met in SIFT-MS analyses and, in addition, because of their biological and environmental significance, which renders them of particular interest. The results of this study show that consistent quantification can be achieved for all these neutral compounds when the complete ion chemistry involved in the analyses is properly accounted for. It is particularly important to account for the involvement in the ion chemistry of hydrated hydronium ions when using H_3O^+ precursor ions and for the presence of hydrated product ions produced when very humid samples are being analyzed. This study also indicates that all three precursor ion species are not always suitable for the analysis of particular compounds but that two of the three can always be used. The classes of compound that are best analyzed by each precursor ion species are also indicated. These results indicate the power of SIFT-MS in minimizing ambiguity and improving the accuracy of on-line, direct analysis of the trace gases in humid air and breath. (Int J Mass Spectrom 209 (2001) 81–97) © 2001 Elsevier Science B.V.

Keywords: SIFT-MS; Trace-gas analysis; Chemical ionization; Precursor ions.

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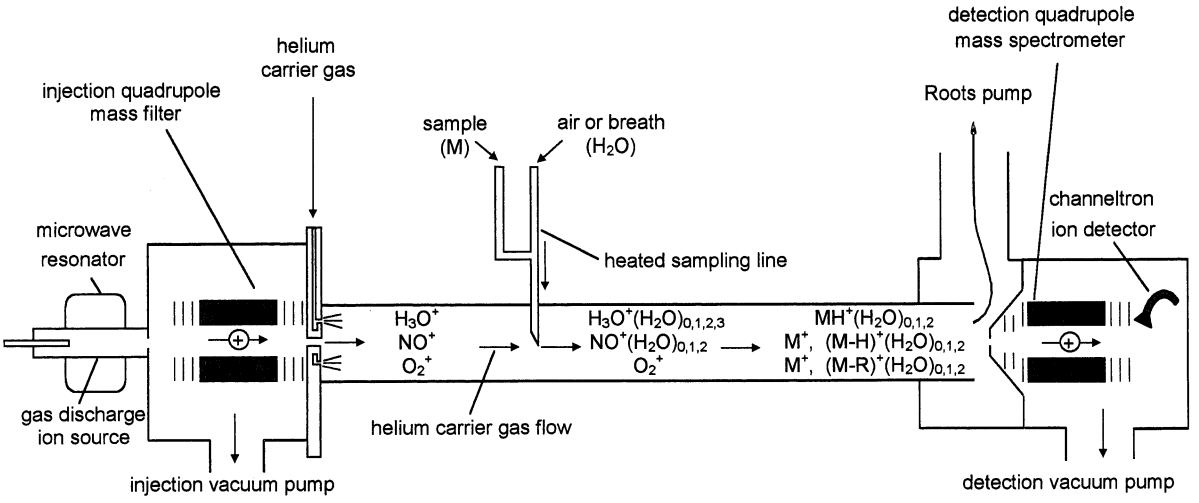

Fig. 1. A schematic diagram of the SIFT-MS instrument. The precursor ions are injected into the helium carrier gas and, with the introduction of water vapor (present in laboratory air and breath), the H_3O^+ and NO^+ ions are partially converted to their hydrates. These various precursor ions then react with the trace-gas molecules, M, producing the types of product ions shown.

1. Introduction

Selected ion-flow tube mass spectrometry, SIFT-MS, is a new analytical method for the detection and quantification of trace gases in humid air and exhaled breath in real time at the parts per billion (ppb) and parts per million (ppm) levels [1,2,3]. It relies on the chemical ionization [4,5] of trace gases to the exclusion of the major air/breath gases (N_2, O_2, CO_2, H_2O, Ar), in fast-flowing helium carrier gas using selected precursor ions, those of choice being H_3O^+, NO^+, and O_2^+ [2,3]. The SIFT-MS instrument set-up is such that each of these precursor ions can be selected individually by the upstream mass filter from a mixture of ions continuously produced in an ion source (see Fig. 1). Thus, each precursor ion species can be used to analyze the trace gases in a particular air/breath sample in less than a minute or so under favorable circumstances without interrupting the flow of the sample into the carrier gas [1]. This facility offers unique advantages over those analytical methods that use only a single ionic species for chemical ionization [4,5,6], as the three precursor ion species undergo different—usually specific—reaction processes with different classes of compounds [7–16]. If the ion chemistry of these precursor ions is fully understood, this greatly assists trace-gas identification [1,2,3]. Our extensive studies of the kinetics (rate coefficients and product ions) of the reactions of these ions with a wide variety of organic compounds have provided this essential knowledge. We enlarge on this theme in later sections of this article. Several different precursor negative ion species recently have been used in a balloon-borne chemical ionization instrument to improve the reliability of quantification of nitric acid in the terrestrial atmosphere, but in this experiment the different negative ion species were formed in separate ion sources [17].

The rapid and accurate quantification of trace gases is achieved by a proper understanding of the carrier gas flow dynamics, primarily the flow speed (hence the reaction time) and diffusion effects [1,18], the sample flow rate into the carrier gas [1], the discrimination in the downstream analytical mass spectrometer (see Fig. 1) against product ions of different masses [18], and the rate coefficients and ionic products of the ion–molecule reactions involved in the analysis [1]. Many of the rate coefficients and ion products that are required are provided by the exten-

sive database that we have created from our detailed studies to which we referred above [19].

When analyzing trace gases in a particular sample using one, two, or three of the suitable precursor ion species, there are parameters involved in the quantification that are obviously common and do not change: the reaction time, the carrier gas flow rate, and the set up of the downstream analytical mass spectrometer. If these parameters are properly described, and if the ion chemistry of the precursor ion with each trace gas in the carrier gas along the flow tube is properly understood, then accurate quantification is assured. Much of our effort has been employed in exploring and fully understanding the varied thermal energy ion chemistry involved in SIFT-MS. This has involved the study of some hundreds of ion–molecule reactions using selected ion-flow tube (SIFT) methods [7–16]. We have given special attention to the influence on these reactions of the relatively large amount of water that is inevitably introduced into the carrier gas along with the trace gases when a sample of humid breath is being analyzed [20].

One check on the validity of the analyses, so reliant on the affirmation of the ion chemistry, is the analysis of a variety of trace gases using the three available precursor ion species; most importantly, including analyses in the presence of humid air and breath. This is the focus of the study described in this article. It is worthy of note that we have previously validated the SIFT-MS analytical method for dry air samples by using the syringe dilution [21] and permeation tube [22] methods to prepare standard mixtures of some organic compounds in dry air. But the influence on the ion chemistry of water vapor at the concentrations found in breath samples can be profound, as our recent article on this topic demonstrated [20].

2. Experimental

A transportable selected ion flow tube, TSIFT, instrument (manufactured to our design by Europa Scientific) located at Keele University and the laboratory SIFT instrument at the Heyrovsky Institute in Prague were used for these experiments. The data were acquired and analyzed using our SIFT-MS software library [19]. Details of the SIFT-MS analytical method have been given in several papers [1–3].

For these experiments, we chose seven different compounds for analysis in the presence of laboratory air of modest humidity (typically 1%) and then breath at relatively high humidity (typically 6%). Each compound was introduced as a trace gas into the helium carrier gas of the TSIFT instrument, and air/breath was added at a flow rate typical of that used for SIFT-MS analyses (see the schematic arrangement of the experiment in Fig. 1). The seven compounds were chosen principally for their chemical diversity but also for their physiological significance. They are ammonia, ethanol, acetone, and isoprene, which are all present in exhaled human breath in varying concentrations in the healthy state [23] and present at elevated levels for various diseased states [24,25], and 1-propanol (liver disorder) [6] and dimethylamine (kidney failure) [26,27], present in breath in a diseased state. Benzene, a minor but common atmospheric pollutant [28], is primarily included as a representative aromatic hydrocarbon. A small drop of the compound to be analyzed was introduced into a resealable plastic bag of 500 mL approximate volume, which was then inflated with dry cylinder air to produce a weak dry air/compound mixture. For ammonia, a drop of a concentrated solution of ammonia in water was used, ammonia still being dominant over water vapor in the air mixture produced. A valuable feature of this SIFT-MS analytical method is that in addition to the analysis of trace gases in air/breath samples at the ppb and ppm levels, the humidity of the sample, typically at the few percent level, can be determined at the same time and can provide an important indicator of the quality of the sample, especially of breath samples [29].

3. Identification of the product ions

The analyses were carried out by first introducing a small flow of the dry air/compound mixture from the sampling bag into the carrier gas at a rate that resulted

in the reduction of the precursor ion count rate at the analytical mass spectrometer by no more than a few percent, as is desirable for SIFT-MS analyses [1]. Following this, laboratory air was introduced into the carrier gas at a flow rate typical of that used for air analysis, and a precursor ion/product ion mass spectrum was obtained by operating the SIFT-MS instrument in the full-scan mode [1,3]. Another mass spectrum was then obtained as the laboratory air was replaced by humid breath (sampled via the same capillary at the same flow rate; see Fig. 1).

The redistribution among the various precursor ions (i.e., $H_3O^+[H_2O]_{0,1,2,3}$, $NO^+[H_2O]_{0,1,2}$) and the various product ions (e.g., M^+, MH^+, $[M–H]^+$ and their hydrates) in the presence of relatively dry laboratory air (in breath analysis corresponding to an inhalation period) and moist air (breath exhalation) periods is very obvious, especially when H_3O^+ is the precursor ion. This is dramatically demonstrated by the spectra shown in Fig. 2a (laboratory air) and Fig. 2b (breath exhalation). Note the obvious conversion of the H_3O^+ ions to the hydrates with the trihydrate at $m/z = 73$ becoming the dominant ion species. Note also the promotion of the $NH_4^+(H_2O)_{0,1,2}$ product ions toward the higher-order hydrates. These spectra are obviously concerned with the analysis of ammonia, which we discuss in detail later. Mass spectra such as those shown in Fig. 2 are used to identify all primary and secondary product ions that must be included in the analysis for accurate quantification. The *m/z* values of the observed product ions are given in Table 1.

4. Quantification of the trace gas

When the correct precursor and product ions involved in the analysis of a particular trace-gas compound have been identified, the actual quantification of the trace gases is achieved using the multi-ion mode [1,3]. In this, the on-line computer performs rapid switching of the analytical mass spectrometer between the precursor and product ions, coupled with ion counting. The count rates of all the ions involved in the analysis are then displayed as a function of time as exemplified in Fig. 2c as, first, laboratory air flows into the carrier gas and then when this is displaced by breath at the entrance to the inlet port. The computer then calculates the trace-gas concentration in the incoming sample in the presence of water molecules as a function of time. The quantification of the trace gas follows from the relative count rates of the product ions to precursor ions according to an expression given in previous publications [20,19], using the rate coefficients given in Table 1 [7,12,14,30–32]. The mean trace-gas concentrations were then obtained by averaging them over the duration of the flow of the laboratory air and of the breath into the helium carrier gas.

This procedure was repeated for all three precursor ions without interrupting the sample flow into the carrier gas. The trace-gas concentration in the carrier gas was determined using each precursor ion species. In this way, direct comparisons are made of the quantification by the three precursor ions. This was repeated several times for different trace gas concentrations. These multi-ion mode analyses can be carried out very quickly (in ~2 min) using the three precursor ions, thus allowing comparative analyses on a given trace gas mixture. The water content of the air was typically at the 1%–2% level, and the water content of the breath was typically 6%. Thus, we observed the influence on the ion chemistry of water molecules in the carrier gas and, especially, their influence on the accuracy of quantification of the various trace gas compounds. We discuss sample data for acetone analysis, shown in Fig. 3, in detail later.

It should be noted that when exhaled breath is introduced into the carrier gas, the concentrations of acetone, ammonia, and isoprene (and sometimes ethanol) are increased somewhat and had to be accounted for by subtracting the breath concentration of these compounds. However, these represented only relatively small contributions (at <1 ppm) compared with the concentrations in the bag reservoirs (see following sections).

5. Preliminary remarks on the ion chemistry

H_3O^+ ions invariably undergo efficient proton transfer reactions with those molecules, M, that have

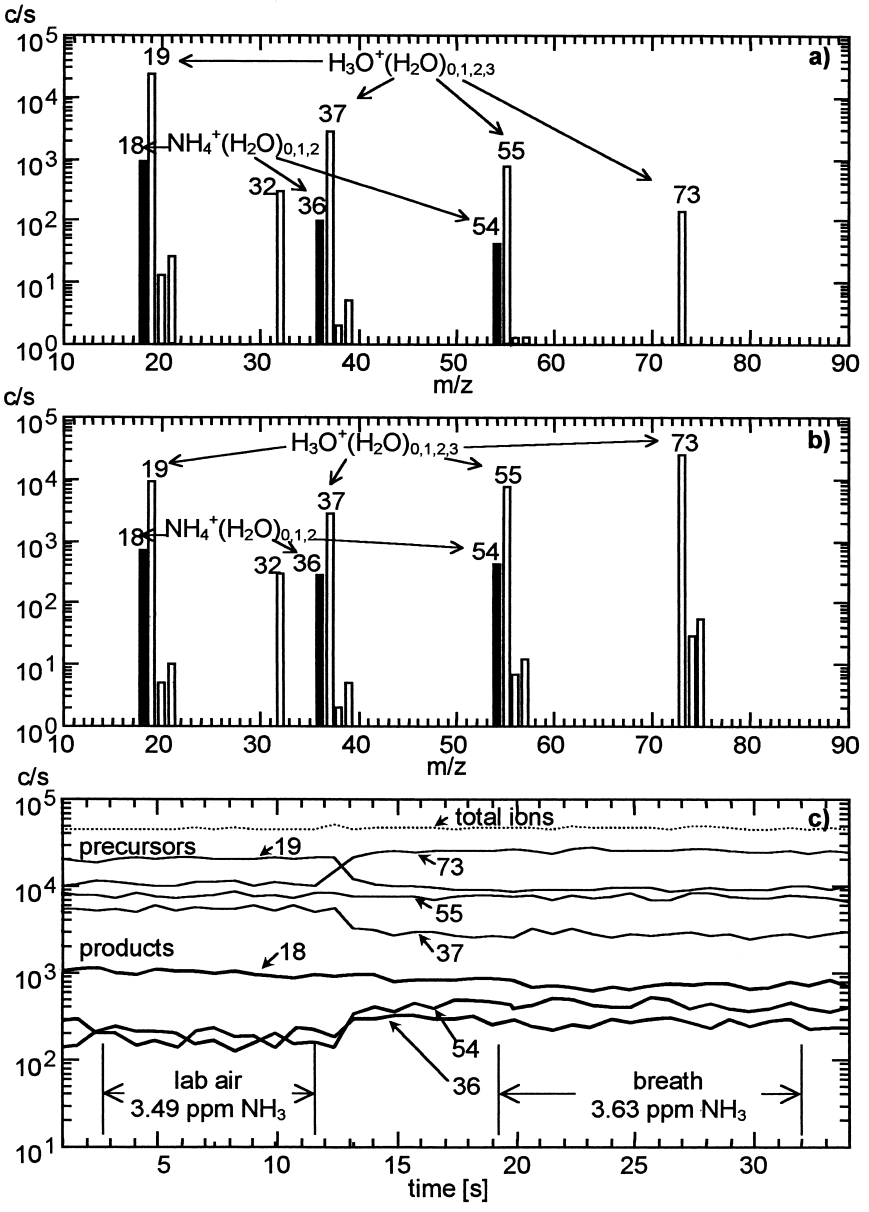

Fig. 2. Mass spectra obtained by operating the SIFT-MS instrument in the full-scan mode using H_3O^+ precursor ions (m/z = 19) when ammonia is introduced into the helium carrier gas simultaneously with (a) humid laboratory air and (b) more humid breath. Note the development of the hydrated hydronium ions at m/z values of 37, 55, and 73 when breath is present and, similarly, the enhanced hydration of the NH_4^+ ions (m/z = 18), producing $NH_4^+(H_2O)_{1,2}$ ions at m/z values of 36 and 54. The impurity ions at m/z = 32 are O_2^+ ions that are formed largely via the action on O_2 molecules of energetic photons from the gas discharge ion source. Note also the appearance of the ^2H and ^{18}O isotopic variants of the $H_3O^+(H_2O)_{0,1,2,3}$ ions. The plots of count rates (c/s) against time for all the ions involved in ammonia quantification shown in (c) were obtained by operating the SIFT-MS instrument in the multi-ion mode, initially with laboratory air (breath inhalation) and then with breath (exhalation) entering the carrier gas. The derived concentrations of ammonia in the incoming air sample (in parts per million) during the inhalation and exhalation phases are also shown.

Table 1
Rate coefficients and product ions used for SIFT-MS analyses of various compounds using the H_3O^+, NO^+, and O_2^+ precursor ions and several of their hydrates

	H_3O^+					NO^+				O_2^+	
	k [10^{-9} cm^3 s^{-1}]					k [10^{-9} cm^2 s^{-1}]				k [10^{-9} cm^2 s^{-1}]	
	k_{19}	k_{37}	k_{55}	k_{73}	Product ions *m/z*	k_{30}	k_{48}	k_{66}	Product ions *m/z*	k_{32}	Product ions *m/z*
Ammonia (17)	2.6[a]	2.5[b]	2.3[b]	2.1[b]	18, 36, 54	. . .[a]	. . .	. . .	. . .[a]	2.4[c]	17, 35
Dimethylamine (45)	2.1[a]	1.8[c]	1.6[c]	1.5[c]	46, 64	1.8[a]	1.6[c]	1.5[c]	44, 45, 62, 63, 75	1.6[a,c]	30, 44, 45, 62, 63
Acetone (58)	3.9[c]	3.3[d]	2.5[d]	2.4[d]	59, 77	1.8[e]	3.0[c]	2.4[c]	88	3.1[e]	43,58, 61, 76
Benzene (78)	2.0[e]	0[f]	0[f]	0[f]	79	1.5[g]	1.4[c]	1.2[c]	78, 108	1.6[c,g]	78
Isoprene (68)	2.0[g]	1.8[d]	0[f]	0[f]	69, 87	1.6[e]	0[f]	0[f]	68, 86	1.6[c]	53, 67, 68, 85, 86
Ethanol (46)	2.7[d,h]	2.3[d]	2.1[d]	0[f]	47, 65, 83	1.2[h]	2.1[c]	1.9[c]	45, 63, 81	2.3[c,h]	Multiple
1-propanol (60)	2.7[c]	2.3[c]	2.2[c]	2.1[e]	43, 61, 79, 97	2.3[h]	2.2[c]	2.1[c]	59, 77, 95	2.2[c,h]	Multiple

[a]Data from [12], note that ammonia does not react with NO^+.
[b]Data from [30].
[c]Calculated collisional rate coefficient [31].
[d]Data from [32].
[e]New SIFT data.
[f]These precursor ions are unreactive with the specified sample but are nonetheless included in the analysis to account for the change in the distribution of the precursor ions caused by the presence of water.
[g]Data from [14].
[h]Data from [7].

proton affinities [33] greater than that of water molecules, thus producing MH^+ ions [32]. Such reactions proceed at the collisional (gas kinetic) rate [34], which can be calculated if the polarizabilty and the dipole moment of M are known [31]. The appearance of MH^+ ions on the SIFT-MS product ion spectrum is, therefore, to be expected (see Fig. 2). Furthermore, it is important to appreciate that when water is present in the helium carrier gas, these MH^+ ions can associate with water molecules producing monohydrate ions $MH^+ \cdot (H_2O)$ and, for some MH^+ ions, the dihydrate ions $MH^+ \cdot (H_2O)_2$ (see following text). Also, successive three-body association reactions partially convert H_3O^+ precursor ions into the hydrated hydronium (water cluster) ions $H_3O^+ \cdot (H_2O)_{1,2,3}$; for example,

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

This is the process in which the hydrated hydronium ions shown in Fig. 2 are formed. These hydrated ions may then behave as additional precursor ions, because they are usually very reactive with polar molecules, undergoing ligand-switching reaction [35] of the kind

$$H_3O^+ \cdot H_2O + M \rightarrow MH^+ \cdot H_2O + H_2O. \quad (2)$$

Hence, in the presence of appreciable concentrations of water molecules, the product MH^+ hydrated ions can dominate the SIFT-MS spectra when H_3O^+ is the precursor ion. Obviously, these adduct ions need to be accounted for in SIFT-MS analyses [1,2,3]. It is worthy of note that, although they sometimes complicate quantification, the presence of such hydrates can be advantageous in that they provide an additional analytical tool for the elucidation of the type of trace-gas molecules present in a sample. We show below, for reasons we now well understand and that we explain, that the water has a major influence on the ion chemistry when H_3O^+ precursor ions are used. We have addressed this important point with respect to the analysis of some polar molecules in a recent paper [20] and showed that when the presence of water is properly accounted for, the quantification of the trace gases is accurate. In this article, we successfully extend this aspect of SIFT-MS work to include nonpolar molecules. We also show that the presence of water molecules has less effect when NO^+ and O_2^+ are the precursor ions, but if the presence of water vapor is ignored in the analysis of some compounds using NO^+ precursor ions, then significant errors in

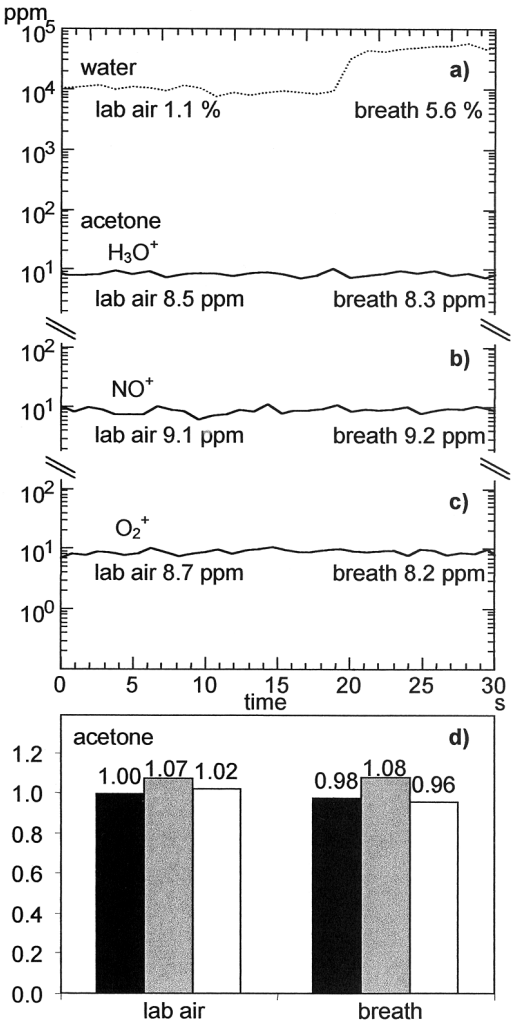

Fig. 3. The derived acetone concentration in an air sample (in parts per million) obtained by SIFT-MS using (a) H_3O^+, (b) NO^+, and (c) O_2^+ precursor ions. Also shown in (a) are the percentage humidity of the laboratory air and breath. The vertical bar charts in (d) show the mean values obtained using H_3O^+ (black), NO^+ (shaded), and O_2^+ (white) normalized to the H_3O^+ laboratory air value.

quantification can be introduced. This complication in the ion chemistry is not nearly so important when O_2^+ precursor ions are used, as these ions do not so rapidly form adduct ions with H_2O molecules. Hence, O_2^+ and NO^+ hydrates are not nearly so important as precursor ions in SIFT-MS analyses. When O_2^+ and NO^+ hydrates are present, they are partially converted to hydrated hydronium ions $H_3O^+ \cdot (H_2O)_{1,2,3}$ in a reaction sequence well understood following detailed research in atmospheric ion chemistry [36].

$NO^+ \cdot (H_2O)_{1,2}$ hydrated ions can partly contribute to the product ion spectra for some types of organic molecules, such as ketones [8]; for example,

$$NO^+ \cdot H_2O + CH_3COCH_3 \rightarrow NO^+ \cdot CH_3COCH_3 + H_2O. \quad (3)$$

This is a ligand-switching reaction like reaction (2). We will see later the importance of the $NO^+ \cdot (H_2O)_{1,2}$ hydrate ions in the quantification of some molecules and, especially, in the quantification of acetone. NO^+ ions undergo efficient hydride ion (H^-) transfer reactions with a variety of organic molecules producing $(M–H)^+$ ions; for example,

$$NO^+ + C_2H_5OH \rightarrow C_2H_5O^+ + NOH. \quad (4)$$

These latter ions are prone to associate with water molecules forming $(M–H)^+ \cdot (H_2O)_{1,2}$ hydrate ions, which are easily recognized on the SIFT-MS product ion spectra.

NO^+ ions also undergo charge transfer reactions with M molecules that have low ionization potentials such as the hydrocarbons [14] producing M^+ ions; for example, with isoprene:

$$NO^+ + C_5H_8 \rightarrow C_5H_8^+ + NO. \quad (5)$$

Similarly, O_2^+ precursor ions invariably undergo charge transfer reactions with M molecules producing parent M^+ ions and additional fragment ions for some open-chain polyatomic molecules [7–16]. When such fragmentation occurs, the value of O_2^+ as a precursor ion for the analysis of complex mixtures such as breath is limited. However, it can still be used to great effect to detect and quantify some stable organic molecules, such as aromatic hydrocarbons and small molecules such as NO, NO_2, and NH_3, as we will see below. It must also be appreciated that some product ions of the O_2^+ and NO^+ charge transfer reactions may also associate with water molecules and that the hydrated ions so formed must be accounted for in SIFT-MS analyses. The detailed knowledge obtained

on these reactions' processes and the ion products of the large number of reactions that we have studied to develop the database [7–16,19] is vital to the proper quantification of trace gases in air and breath using SIFT-MS.

6. Results of these studies of the quantification of trace gases

In this section we demonstrate the care that is needed for accurate quantification of trace gases using SIFT-MS by discussing the details of the ion chemistry involved in the analyses of the seven compounds included in this study, using the H_3O^+, NO^+, and O_2^+ precursor ions. As we will show, it is not possible to use all three precursor ions for the analysis of some compounds, and it is impractical for the analysis of some others. We begin by describing the analysis of ammonia, which involves the simplest ion chemistry.

6.1. Ammonia

This relatively simple molecule is very water soluble, and as such, its accurate quantification has proved difficult in the presence of water [37]. It is present at high levels in the breath of patients suffering from renal failure [25], and this has been a serious motivation in our efforts to accurately quantify this trace gas. SIFT-MS handles its quantification very well [37]. H_3O^+ ions undergo rapid proton transfer reaction with NH_3 molecules, producing NH_4^+ ions. The hydrated hydronium ions, inevitably present when breath is being analyzed, react rapidly with NH_3 molecules via proton transfer and ligand switching (see reaction [2]), producing $NH_4^+(H_2O)_{0,\,1,\,2}$ hydrate ions [30,32], and so, for accurate analyses, the product ions at *m/z* values of 18, 36, and 54 must be included in the analysis. A sample SIFT-MS spectrum is shown in Fig. 2b for the analysis of ammonia in the presence of breath using H_3O^+ precursor ions.

A multi-ion mode data trace during a breath inhalation/exhalation cycle using H_3O^+ precursor ions is shown in Fig. 2c. Note the obvious redistribution among the $H_3O^+ \cdot (H_2O)_{0,1,2,3}$ ions between the inhalation (laboratory air) and exhalation (breath) phases. Yet the ammonia analysis results in essentially the same parts per million value (having accounted for the additional endogenous ammonia introduced in the breath sample, which is readily separately determined [37]). A vital point to appreciate here is that the conversion of the H_3O^+ ions to its hydrates is a continuous process along the reaction zone (water entry port to mass spectrometer sampling orifice; see Fig. 1). Thus, in effect, the precursor ions are changing along the reaction zone, and this phenomenon must be accounted for in the analysis of the ammonia concentration and, indeed, in the analyses of all other trace-gas species, even those that do not react with the H_3O^+ hydrates, such as benzene (see following text). This is achieved using our refined analysis, which we have described in detail and for which we have demonstrated its efficacy in our recent paper [20].

It is well known that NO^+ ions do not react at an appreciable rate with NH_3 [12], and so, they cannot be used as precursor ions for ammonia analysis. However, O_2^+ ions undergo rapid charge transfer with NH_3 molecules, producing only NH_3^+ parent cations at $m/z = 17$. The product NH_3^+ ions only slowly associate with H_2O molecules, producing $NH_3^+ \cdot H_2O$ ions at $m/z = 35$, but these ions must be included as product ions for accurate SIFT-MS analyses of ammonia in moist air.

The mean relative values of ammonia concentrations, as determined using H_3O^+ and O_2^+ ions on several samples at different concentrations in the presence of laboratory air and then more humid breath, are shown in the vertical bar charts in Fig. 4a. The normalization to the H_3O^+ laboratory air analyses does not imply that these are inherently more accurate; this caution also applies to all the analyses of the other compounds presented in this article. The good agreement of the H_3O^+ and O_2^+ quantification is immediately obvious, being within our usually quoted 10% estimated uncertainty. All of the apparent difference can be accounted for by the uncertainty in the critical rate coefficients for the several ion–molecule reactions that must be included in the analytical procedure. The actual values of the rate coefficients

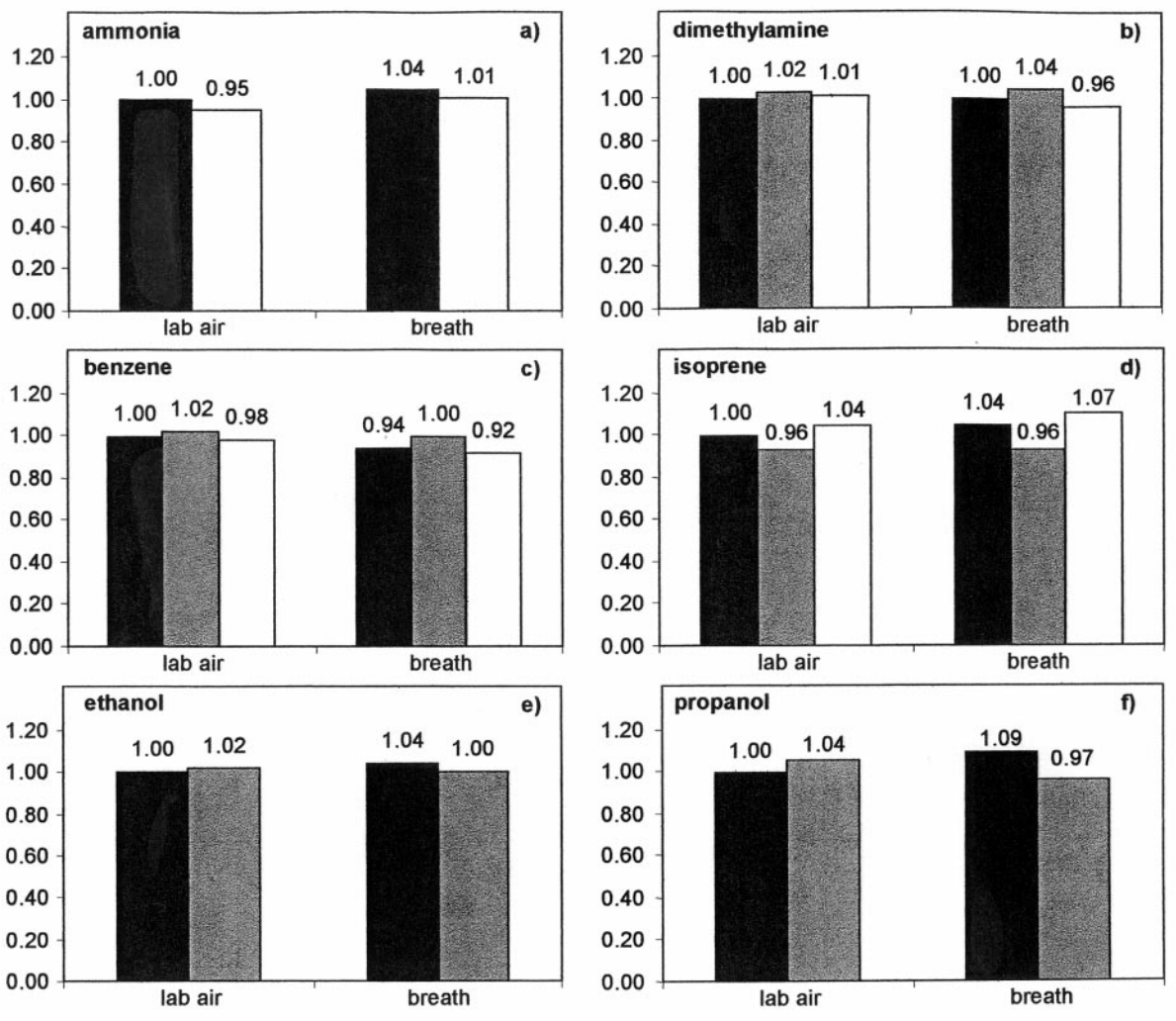

Fig. 4. Vertical bar charts of derived concentrations (analogous to those shown in Fig. 3[d]) of the six compounds indicated, using H_3O^+ (black), NO^+ (shaded), and O_2^+ (white) precursor ions with laboratory air and breath sampled into the carrier gas. The mean values are normalized to the mean H_3O^+ laboratory air value.

included in the analyses of ammonia and of the other compounds included in this study are given in Table 1. The absolute rate coefficients cannot be measured to better than 15% [12,38], but the relative values can be measured to ~10% [12]. The good agreement indicated in Fig. 4a shows that we have properly accounted for all the ion chemistry involved in ammonia quantification. This method for direct, on-line ammonia analysis is proving to be of great value in renal science [25].

6.2. Dimethylamine

This secondary amine, like ammonia, is present in the breath of those suffering from renal failure [26,27]. It reacts with H_3O^+ ions by simple proton transfer, producing $(CH_3)_2NH_2^+$ ions at $m/z = 46$ at the gas kinetic rate [12]. The $H_3O^+(H_2O)_{1,2,3}$ hydrate ions also react rapidly with this amine, but only the monohydrate ion $(CH_3)_2NH_2^+ \cdot H_2O$ at $m/z = 64$ is apparently formed in significant fractions. Thus, the

$H_3O^+(H_2O)_{0,1,2,3}$ ions are the precursors, and the product ions are at *m/z* values of 46 and 64, respectively, and only these need to be included in the analyses.

The reaction of NO^+ ions with dimethylamine results in two primary product ions, the major product $(CH_3)_2NH^+$ at $m/z = 45$ due to charge transfer (as in reaction [5]) and the minor product $(CH_3)_2N^+$ at $m/z = 44$ due to H^- transfer (as in reaction [4]) [12]. Both these primary product ions also form hydrates that appear as minor products at *m/z* values of 62 and 63, but do so only at measurable levels when humid breath is present. Further, a small signal (~4% of the total product ion signal) is present at $m/z = 75$. This can only be the adduct ion $NO^+ \cdot (CH_3)_2NH$. Although its formation by direct three-body association cannot be entirely ruled out, it is most probably formed in the switching reaction

$$NO^+ \cdot H_2O + (CH_3)_2NH \rightarrow NO^+ \cdot (CH_3)_2NH + H_2O. \quad (6)$$

Although these three hydrate ions at *m/z* values of 62, 63, and 75, respectively, together represent only ~10% of the total product ions, for this comparative exercise they are included in all the analyses. For the analyses of complex mixtures such as breath they could be excluded without incurring serious errors.

The reaction of O_2^+ ions with $(CH_3)_2NH$ again results in two primary product ions, the major one being $(CH_3)_2NH$

generally known is that ethanol occurs naturally in blood and breath [46], principally because of its production by bacteria in the gut. Ethanol reacts with H_3O^+, forming only the protonated molecule $C_2H_5OH_2^+$ at *m/z* = 47 [7]. The hydrated ions $H_3O^+ \cdot (H_2O)_{1,2}$ undergo rapid switching reactions with ethanol, producing $C_2H_5OH_2^+ \cdot (H_2O)_{1,2}$ hydrates at *m/z* values of 65 and 83, but the trihydrate $H_3O^+ \cdot (H_2O)_3$ does not react with ethanol [32]. However, the latter ion must be included as an unreactive precursor ion in the analysis, especially when humid breath samples are being analyzed. The precursor and product ions included in the analyses, along with the appropriate rate coefficients, are included, as before, in Table 1.

NO^+ ions react with ethanol molecules via H^- transfer, resulting in $C_2H_5O^+$ ions at *m/z* = 45 [7]. The hydrated ions $C_2H_5O^+ \cdot (H_2O)_{1,2}$ at *m/z* values of 63 and 81 are also observed. The $NO^+ \cdot (H_2O)_{1,2}$ ions that are formed when humid air is introduced into the helium carrier gas also react with ethanol, but no additional product ions are observed, except for a very weak signal at *m/z* of 76 (i.e., $NO^+ \cdot C_2H_5OH$), but this was too small to be included in the analyses. The NO^+ hydrates were included along with NO^+ as the precursor ions for the analysis. So the product ions are at *m/z* values of 45, 63, and 81 only (see Table 1).

In our previous paper concerning the reactions of several alcohols with O_2^+ ions, we reported that the primary products of the O_2^+/ethanol reaction were only $C_2H_5O^+$ ions and $C_2H_6O^+$ ions at *m/z* values of 45 and 46, respectively [7]. The present studies have revealed that we missed a third significant ionic product—CH_2OH^+ at *m/z* = 31. There are also other minor product ions at *m/z* values of 42 and 43, although these may result from the reaction of ethanol with the small fractions of metastable O_2^+ ions that are injected into the helium as described previously (see the previous section on dimethylamine). To further complicate this situation, the major product ions also form hydrates, so to perform an analysis of ethanol using O_2^+ ions is prohibitively complicated. This is also the case for the analysis of 1-propanol, as we discuss later. Indeed, we judge that as a general principle, O_2^+ is not a suitable precursor ion for the analysis of alcohols in SIFT-MS. An interesting point is that the product ion at *m/z* = 31 behaves like protonated formaldehyde, as is implied above by the written structure, rather than like the isomeric CH_3O^+ methoxy cation. We can substantiate this deduction following our detailed study of the reactions of H_3O^+ with CH_2O and of CH_2OH^+ with H_2O [47], in which we show that the $CH_2OH^+ \cdot H_2O$ hydrate ion reacts endothermically with H_2O to produce $H_3O^+ \cdot H_2O$ ions. The ion at *m/z* = 31 formed in the O_2^+/C_2H_5OH reaction and its hydrate at *m/z* = 49 are seen to behave in this precise way.

The comparative data obtained for the analysis of ethanol using H_3O^+ and NO^+ precursor ions are presented in Fig. 4e, when both laboratory air and breath are present in the helium carrier gas. As can be seen, the agreement in the analyses for the two precursor ions is very good at the different water molecule concentrations, which indicates again that the ion chemistry and the kinetics have been described properly.

6.7. 1-Propanol

On protonation by H_3O^+, 1-propanol, C_3H_7OH, largely dissociates (releasing an H_2O molecule) to give $C_3H_7^+$ hydrocarbon ions at *m/z* = 43, with only a small fraction (10%) remaining intact as $C_3H_7OH_2^+$ ions at *m/z* = 61 [7]. In common with most hydrocarbon ions, the $C_3H_7^+$ ions do not readily form hydrates, but according to our SIFT experiments, the $H_3O^+ \cdot (H_2O)_{1,2,3}$ hydrate ions all react rapidly with 1-propanol molecules, producing $C_3H_7OH_2^+ \cdot (H_2O)_{1,2}$ hydrate ions at *m/z* values of 79 and 97 (compare this with the corresponding ethanol reactions discussed above). Thus, the analysis of this alcohol in moist air/breath is performed by the refined analysis with $H_3O^+ \cdot (H_2O)_{1,2,3}$ precursor ions and the four product ions at *m/z* values of 43, 61, 79, and 97 (see Table 1).

NO^+ reacts with 1-propanol via H^- transfer to produce $C_3H_7O^+$ ions at *m/z* = 59 [7]. In the presence of the water molecules, the hydrate ions $C_3H_7O^+ \cdot (H_2O)_{1,2}$ are formed at *m/z* values of 77 and 95. It is interesting to note that the *m/z* = 59 ion formed in this reaction clearly forms a dihydrate

unlike the isomeric protonated acetone (also m/z = 59), which only forms a monohydrate under SIFT-MS conditions, as indicated previously. A tiny signal (<1%) at m/z = 90 would appear to indicate that partial switching or association of NO^+ with C_3H_7OH is occurring, forming $NO^+ \cdot C_3H_7OH$ adduct ions. However, these product ions were not included in the analysis.

As mentioned previously, the reaction of O_2^+ with 1-propanol is far too complex to be used for analysis in SIFT-MS, as it leads to more than five product ions and their hydrates. We, therefore, do not include this reaction in the comparative study.

The comparative data obtained for the analysis of 1-propanol using H_3O^+ and NO^+ precursor ions are presented in Fig. 4f for laboratory air and breath samples present in the carrier gas. As can be seen, the agreement for these two precursor ions for the analysis of this alcohol also is acceptably good even when the water molecule number density is high (breath present), which again indicates that the ion chemistry and the kinetics have been properly described.

7. Discussion and concluding remarks

These studies were carried out principally to demonstrate that accurate quantification of a wide variety of trace gases in humid air and breath, that is, in the presence of relatively large number densities of water molecules, can be accomplished by SIFT-MS, using H_3O^+, NO^+, and O_2^+ precursor ions, when the gas phase ion chemistries involved are fully understood. The background ion chemistry has been researched for several years to provide the required kinetic data and, thus, to establish an extensive database for SIFT-MS [19]. However, this is an on-going process: additional new information has been obtained from this study, especially relating to the hydration of ions, that usefully extends the database.

The good agreement in the quantification of the several trace gases included in this study, using the three different precursor ion species, which involve quite different ionic reaction processes, demonstrates that for these compounds, we have indeed correctly identified the ionic reactions that occur. Particular attention has been given to the role of the water vapor in the ion chemistry and the production of hydrates of the precursor ions, as these can become the dominant precursor ions. This is especially so when H_3O^+ precursor ions are used. Then the various $H_3O^+ \cdot (H_2O)_{0,1,2,3}$ hydrated ions, which form sequentially along the SIFT-MS reaction zone, also act as the precursor ions, and then it is essential to know which of these hydrates react with each trace gas to be quantified. For example, all four $H_3O^+ \cdot (H_2O)_{0,1,2,3}$ ions react rapidly with most polar molecules (such as acetone and the propanol isomers), but the nonpolar aromatic hydrocarbons react only with H_3O^+ and not with its hydrates. The good news is that this apparently complex kinetic situation is handled very well by our previously reported refined analysis [20] and provides accurate quantification of these chemically diverse organic and inorganic compounds. $NO^+ \cdot (H_2O)_{1,2}$ hydrate ions are much less efficiently formed under SIFT-MS conditions, even when the water molecule number density in the helium carrier gas is relatively high, but these ions must sometimes be considered as precursor ions, as we have shown. However, $O_2^+ \cdot (H_2O)_{1,2}$ ions are always insignificant under SIFT-MS conditions.

A practical conclusion that emerges from this study is that all three of the available precursor ions for SIFT-MS analyses, H_3O^+, NO^+, and O_2^+, are not always suitable for the quantification of a particular trace gas. H_3O^+ precursor ions are the most versatile, but the change in the distribution of the precursor ions that occurs when humid air is being analyzed (because of the inevitable formation of hydrated hydronium ions) complicates the ion chemistry. However, this is not a serious constraint, and the use of H_3O^+ ions does provide vital extra information on the water content of the sample being analyzed [29].

NO^+ is a most valuable and versatile precursor ion that does not efficiently form hydrates and that generally reacts with most organic compound to form a single product ion. Thus, it can be used widely for SIFT-MS analyses. However, it sometimes reacts via three-body association, for example, with ketones, the rates of this type of reaction being both pressure and

temperature dependent. So the pressure and the temperature of the helium carrier gas must be carefully controlled and recorded when such reactions are being exploited for trace-gas quantification.

O_2^+ ions are valuable as precursors because they do not form hydrates to a significant extent and because they are especially valuable for the detection and quantification of small inorganic molecules such as NO, NO_2, and NH_3, which do not react at significant rates with either H_3O^+ or NO^+ ions. These ions can also be used for some organic compounds that do not fragment appreciably following the charge transfer reactions that form the product ions. Acetone and benzene fall into this category. Indeed, O_2^+ precursor ions are very useful for the detection and quantification of most volatile aromatic hydrocarbons. But these ions are not of practical use for the quantification of alcohols and other hydroxy compounds because of the multiple product ions that are formed, but for these compound types, H_3O^+ and NO^+ are ideal precursor ions in SIFT-MS analyses.

The important message that emerges from this study is that most types of organic and inorganic species that are likely to be met in SIFT-MS analyses can be identified and quantified using at least two of the three available precursor ions. We have shown that consistency is realized in the quantification using two or three precursor ions when the ion chemistries involved are fully appreciated. Discrepancies in these quantifications are typically $<10\%$, which mostly reflects the uncertainty in the relative rate coefficients used in the analyses. This ease of use of two or three precursor ions for analyzing the same sample is the great advantage SIFT-MS has over most other trace-gas analytical methods. This reduces the likelihood of erroneous trace-gas identification and quantification, a goal for which we strive when using SIFT-MS in medicine (breath and headspace analyses). Another important point that must not be overlooked is that direct analyses of trace gases in humid air and breath can be achieved without the need for preconcentration or for the removal of water from samples, thus avoiding the dangers inherent in such procedures.

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