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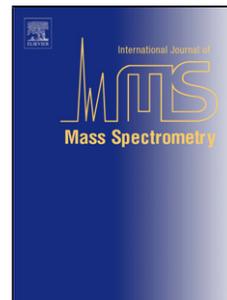
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A potential method for comparing instrumental analysis of volatile organic compounds using standards calibrated for the gas phase

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Graphical abstract
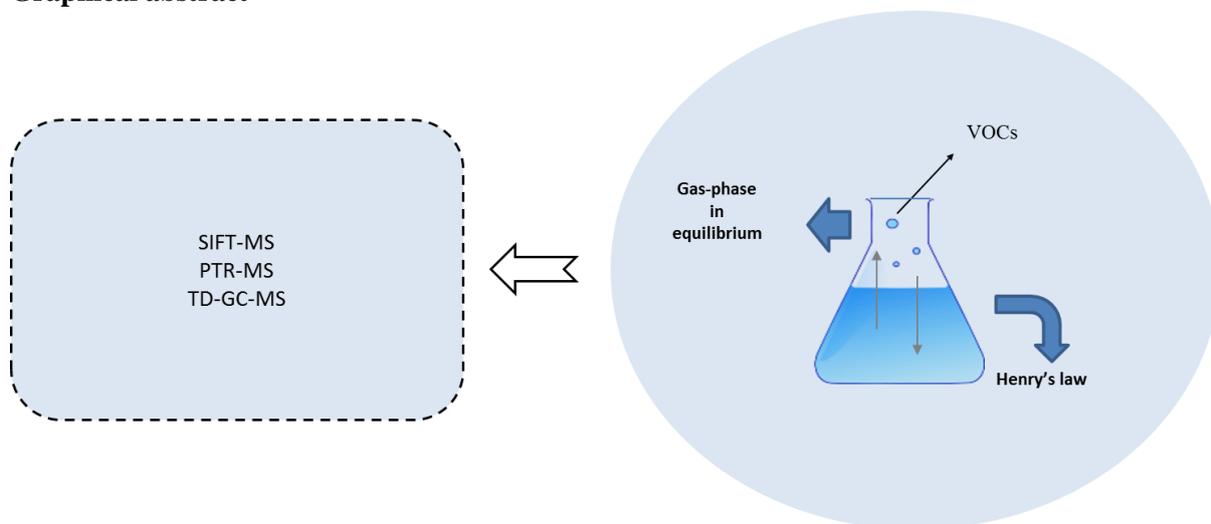
Highlights

- The performance of the instruments was assessed in the analysis of volatiles.
- Rate coefficients were calculated via Su and Chesnavich trajectory theory.
- Estimation of concentration is sensitive to changes in the reduced electric field.

Abstract

In this paper we report a method for the comparative analysis of volatile organic compounds (VOCs) at physiologically representative concentrations by different analytical methods. Standard aqueous solutions of acetone, ethanol, methanol, 1-propanol, 2-propanol and acetaldehyde were prepared by adding a specific mass of compound to a known volume of water, calculated using published Henry's law constants for individual compounds. Headspace concentrations are thus known from established partitioning from dilute aqueous phase in accordance with Henry's law. Selected Ion

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Flow Tube Mass Spectrometry (SIFT-MS), Proton Transfer Reaction Mass Spectrometry (PTR-MS), and Gas Chromatography–Mass Spectrometry (GC-MS) coupled to thermal desorption have been used to study and evaluate the performance of the instruments in the analysis of these VOCs. These analytical techniques have been widely used in the identification and quantification of trace concentrations of VOCs in biological samples. Quantitative determination of VOC concentration was achieved and the performance of the instruments compared with one another. Calibration curves are given within the range 10^1-10^3 ppbv.

Keywords: trace gas analysis; SIFT-MS; PTR-MS; GC-MS; selected ion flow tube mass spectrometry; proton transfer reaction mass spectrometry.

1. Introduction

Considerable efforts have been undertaken to develop non-invasive diagnostic methods for detecting and monitoring disease through the analysis of volatile organic compounds (VOCs) which can potentially be used as biomarkers. These VOCs have been detected in exhaled breath, skin emanations, saliva, urine and faecal headspace [1]. Breath analysis in particular has recently become a topic of interest for its potential to provide a non-invasive screening tool in early disease diagnosis [2]. However such measurements have been limited by inconsistent evaluations of the concentrations of such VOCs by different instruments even when they are collected under identical conditions. This shows that the lack of standardization between techniques is still a major challenge due to the vast disparity in the analytical tools employed; the sampling technique itself and the rich chemical diversity of the biological sample at varied concentrations [3].

Recent technological advances in analytical techniques allow the measurement of VOCs at trace concentrations with high sensitivity and selectivity. The analytical techniques most used up to now include, Gas Chromatography–Mass Spectrometry (GC-MS), Selected Ion Flow Tube Mass Spectrometry (SIFT-MS), and Proton Transfer Reaction Mass Spectrometry (PTR-MS) [4-6].
Gas Chromatography–Mass spectrometry (GC-MS) has been recognised as the gold standard of analytical methodologies for many scientific tests. Its fundamental ability to effectively perform a qualitative analysis enables the identification of isomers within the sample which would be hard or nearly impossible to detect using a mass spectrometer alone (i.e. without GC separation).

However, debatable issues have come through the use of gas chromatography as a quantitative method of VOCs analysis, particularly if a thermal desorption system or Solid Phase Micro Extraction (SPME) is used. Usually, the concentration of the substances of interest is too low for the direct measurement of a gas sample, and therefore enrichment on suitable adsorbents is necessary. In thermal desorption, the concentrated volatile components are desorbed by rapid heating of the adsorption tube, injected and stored in a cold trap, and subsequently, these are transferred to the GC column by rapidly heating the cold trap. This two-step desorption might have a crucial impact on the volatiles detected, i.e., competitive binding and desorption, not to mention thermal-lability of the VOCs.

Classic calibration in GC-MS systems frequently uses a calibration standard or a standard mixture at different concentrations [7-8], however this method does not correct for any variation in the recovery of analytes by thermal desorption sampling techniques. The use of an internal standard improves accuracy and corrects for any variation in the recovery of analytes. In general, the internal standard approach is used to determine the concentration of an unknown sample investigated by GC-

MS. The standard itself must not be present in the original sample and must be rapidly cleaned up from the column. Therefore, isotopically labelled standards should ideally be used [8] and thermal desorption procedures are generally calibrated using internal standard addition using deuterated toluene [7], where standard solutions are prepared and small volumes (typically 0.2 - 2 μl) loaded into each thermal desorption tube individually.

In the SIFT analytical technique, it is possible to carry out ion-molecule reactions under thermal conditions, where the kinetic behaviour is well known [9]. Therefore, quantification of VOCs in air is achieved by using an in-built kinetics library, although it is good practice to periodically check the quantification using known standards [10]. In contrast to SIFT-MS in PTR-MS the underlying ion chemistry is often not known, specifically, the kinetics of the ion-molecule reactions and reaction time are not well established and can be very sensitive to changes in the ratio *E/N,* where *E* is the electric field strength and *N* is gas number density in the reaction chamber [11]. Thus, careful calibration of the instrument is usually carried out for each VOC and is presently the preferred method to ensure accurate quantification [12]. Nevertheless, quantification of VOC concentrations may be accomplished if proton transfer reaction rate coefficients are known [12-13]. Although accuracy may not be as good, in cases where regular and routine calibration using standards is difficult, it may be a reasonable alternative if reaction rate coefficients are known. Quantification is directly dependent on the proton transfer rate coefficient, therefore it is essential to stress the importance of the gas-phase ion chemistry studies on ion-molecule reactions. Theoretical determination of sample concentration via PTR-MS expressed in ppbv, may be theoretically accomplished and this is reported in literature by Beauchamp and co-workers [12].

This paper proposes a method to compare these three analytical techniques, for the analysis of VOCs, through the use of standards calibrated for the gas-phase at physiologically representative concentrations.

2. Experimental details

2.1 Henry's law

Accurate creation of partial pressures of volatile compounds in the headspace is an essential requirement for a correct determination of VOC concentration. Thus, this requires understanding of liquid-phase/gas-phase equilibrium, commonly known as Henry's law [14]. At a constant temperature, the molar concentration of the compound in the liquid is directly proportional to its vapour pressure in the gas phase, as long as the solution is dilute and the gas pressure is low. The relationship for each individual compound is described Henry's constant, k_H. Generally, more volatile compounds have a lower Henry's constant. Henry's constant is temperature dependent, typically increasing with temperature at low temperatures [15]. Temperature corrections are therefore necessary to take into account, as well as ensuring the equilibrium of the system, thus avoiding pitfalls and design errors. Special attention must be paid to chemically reacting systems such as organic acids, which dissociate in the aqueous phase through a reversible equilibrium [15]. To calculate Henry's constants via the method described previously the following equation is applied:

$$k_H = k_H^\circ \times \exp\left(\frac{-\Delta_{sol}H}{R}\left(\frac{1}{T} - \frac{1}{T^\circ}\right)\right) \qquad (1)$$

$$\frac{dlnk_H}{d\left(^1/_T\right)} = \frac{-\Delta_{sol}H}{R} \qquad (2)$$

Here, k^o_H represents the Henry's law constant for solubility in water at 298.15 K; $-\Delta_{sol} H/R$ is the temperature dependence parameter with R being the ideal gas constant and $\Delta_{sol} H$ being the enthalpy of solution; T° is the standard temperature of 298.15 K; and T is the actual temperature. In this work, the values k^o_H and $dlnk_H/d(1/T)$ are given in Table 1. This approach is reasonable for systems where temperature variations do not exceed 20 K, and for compounds soluble in water. Other predictive models are used to estimate the vapour-liquid equilibrium properties, such as the UNIFAC model or computational methods based on quantum chemical calculations, although some models are designed for 298 K only [16-18]. Furthermore, Henry's law constant may be experimentally determined, where dynamic methods (e.g. inert gas stripping method) [19-20] and static equilibration techniques [21-22] are described in literature.

2.2 Samples

Standard aqueous solutions of six VOCs, acetone, ethanol, methanol, 1-propanol, 2-propanol and acetaldehyde were created to produce headspaces containing known concentrations of these compounds in the vapour phase, as calculated using the measured temperature and Henry's constant (k_H) (Table 1). Aqueous solutions were prepared using accurate micropipettes and calibrated for the headspace (10 ppm) at 293 K. Individual one litre solutions (10 ppm) were prepared as follows: 29 µl acetone, 156 µl ethanol, 112 µl methanol, 158 µl 1-propanol and 149 µl 2-propanol were added to individual clean glass bottles and purified (deionised) water was added to obtain 1 litre solutions. These solutions were used to provide more dilute solutions. Diluted solutions were prepared individually, the volumes 250 ml, 50 ml and 5 ml were added to 500 ml glass bottles to provide more dilute solutions that were expected to give headspace concentrations of 5 ppm, 1 ppm and 0.1 ppm respectively. The 500 ml volume was adjusted using purified (deionised) water. A more concentrated solution of acetaldehyde (1000 ppm) was prepared, where 1000 µl of acetaldehyde were added to a clean glass bottle containing 1 litre of purified (deionised) water. This concentrated solution (1000 ppm) was used to provide more dilute solutions of acetaldehyde. Diluted solutions were prepared individually, the volumes 5000 µl, 2500 µl, 500 µl and 50 µl were added to 500 ml glass bottles to provide more dilute solutions that were expected to give headspace concentrations of 10 ppm, 5 ppm, 1 ppm and 0.1 ppm respectively. Experiments with VOC mixtures (section 3.3.3) (i.e. with all compounds mixed in a single bag for comparison and analysed by GC-MS) were prepared according to the following description. One litre solution (10 ppm) was prepared as follows: 28 µl acetone, 156 µl ethanol, 112 µl methanol, 158 µl 1-propanol, 149 µl 2-propanol and 10 ml from the solution of acetaldehyde 1000 ppm, were added to a clean glass bottle and the volume adjusted with purified (deionised) water. One litre solution (5 ppm) was prepared as follows: 14 µl acetone, 78 µl ethanol, 56 µl methanol, 79 µl 1-propanol, 74 µl 2-propanol and 5 ml from the solution of acetaldehyde 1000 ppm, were added to a clean glass bottle and the volume adjusted with purified (deionised) water. One litre solution (1 ppm) was prepared as follows: 10 ml from a concentrated solution of acetone 100 ppm (286 µl/ litre deionised water), 16 µl ethanol, 12 µl methanol, 16 µl 1-propanol, 15 µl 2-propanol and 1000 µl from the concentrated solution of acetaldehyde 1000 ppm, were added to a clean glass bottle and the volume adjusted with purified (deionised) water. A solution of 500 ml (0.1 ppm) was prepared as follows: 500 µl from a concentrated solution of acetone 100 ppm (286 µl/ litre deionised water), 5 ml from the solution of ethanol 10 ppm (156 µl/ litre deionised water), 5 ml from the solution of methanol 10 ppm (112 µl/ litre deionised water), 5 ml from the solution of 1-propanol 10 ppm (158 µl/ litre deionised water), 5 ml from the solution of 2-propanol 10 ppm (149 µl/ litre deionised water) and 50 µl from the concentrated solution of acetaldehyde 1000 ppm, were added to a clean glass bottle and the volume adjusted with deionised water. The reproducibility of standard

generation was determined by preparing five solutions of 2-propanol 10 ppm in the headspace, and these solutions were analysed via SIFT-MS. The standards were prepared with a coefficient of variation determined at 6%. The coefficient of variation is calculated as the ratio of the standard deviation to the mean.

For the analysis by SIFT-MS, the calibration standards were placed (5 ml each), individually, inside a 40 cm long Nalophan sampling bag, made up of 65 mm diameter Nalophan NA tubing 25 μm thick (Kalle UK). Regarding the analysis by PTR-MS, the same procedure was used, although, in this case the sample was placed inside a 45 cm long Nalophan sampling bag, made up of 135 mm diameter Nalophan NA tubing, 25 μm thick (Kalle UK). Previous data (not shown) show that as long as there is enough VOC sample to maintain equilibrium so the VOC of interest is not depleted, the size of the bag does not affect the equilibrium headspace. The solutions for PTR-MS headspace were transported from the Open University to University of Birmingham in DURAN® glass bottles, so the same solution could be used for SIFT-MS and PTR-MS. All the sample bags were sealed and filled with hydrocarbon free air (Air Products) to generate the VOC headspace, or N_2 (BOC Gases, UK) for the PTR-MS measurements respectively.

The headspaces were allowed to equilibrate at room temperature (20 ℃) for 15 minutes for 65 mm diameter Nalophan and 60 minutes for 135 mm diameter Nalophan, and further analysed. The equilibration time varies depending on the size of the bag, thus there is the need to guarantee that VOC are in equilibrium in the gas-phase, and will produce the accurate headspace concentration no matter the size of the bag. Therefore each headspace profile was tracked using the multiple ion monitoring (MIM) mode capability of SIFT-MS to ensure equilibrium in the gas-phase. In the PTR-MS instrument individual sample bags of each VOC were tracked over the time and the headspaces were allowed to equilibrate at ambient air temperature for 60 minutes. The ambient air temperature in the laboratory was measured simultaneously with experiments undertaken, and laboratory temperature was found to be higher than 20 ˚C in some cases. The temperature significantly influences VOC concentration in the headspace, therefore, concentrations were corrected for the ambient air temperature in the laboratory at 20 ˚C. The reproducibility of the sampling procedure was evaluated by preparing five sampling bags (40 cm long Nalophan sampling bag, made up of 65 mm diameter Nalophan NA tubing 25 μm thick) containing 5 ml of the same solution (2-propanol 10 ppm) calibrated for the headspace. Thus, the reproducibility of the sampling procedure was determined by determining the coefficient of variation which in this case was 3%.

2.3 SIFT-MS

The SIFT analytical technique has been described in detail previously by Smith and co-workers [10].

Data were collected using the Mk2 instrument (PDZ Europa, UK) with a flow rate corresponding to a pressure of 0.008 Torr. The sample bags were attached to a heated capillary and analysed using the multiple ion monitoring mode in which individual ions are targeted. The concentrations of the volatiles were automatically determined *at thermal conditions* using an on-line kinetics database containing reaction rate coefficients, developed from numerous detailed selected ion flow tube studies of various classes of compounds (alcohols, aldehydes, ketones, hydrocarbons, *etc*.) with the three precursor ions [25].

2.4 PTR-MS

The PTR-MS principle is well documented and reported by Lindinger and co-workers [26].

Analysis was carried out using a commercial PTR-MS (Kore Technology Limited) equipped with a time-of-flight mass analyzer (drift tube length = 9.04 cm) and using hydronium ions (H_3O^+) which react with gaseous samples. The drift tube working conditions (pressure and reduced electric field) were set to deliver the highest signal of protonated product ion (our findings indicated that theoretical quantification via PTR-MS is sensitive to alterations in the reduced electric field (i.e. changes in the *E/N* ratio) and significantly influences the quantification of compounds in the gas-phase); the drift tube temperature (373.15 K) was kept constant over the experiments. The drift chamber parameter settings (voltage, pressure and *E/N*, where *E* is the electric field strength and *N* is gas number density in the reaction chamber; Td = Townsend, where 1 Td = 1.0×10^{-17} cm^2 V) are listed in Table 2.

Mass spectra were typically collected in the range *m/z* 20 to *m/z* 250 with an integration time of 1 minute. The concentrations of the volatiles were determined through the theoretical prediction of reaction rate coefficients.

2.5 TD-GC-MS

Volatile organic compounds were pumped into pre-conditioned stainless-steel TD sorbent tubes for 5 minutes at a constant flow of 100 ml min^{-1} (Pump TSI Inc. SidePak Model SP730), configured so that the sorbent tube was attached to the pump at one end and the headspace bag at the other, thus the headspace did not pass through the pump itself. The tubes were pre-conditioned with dual packing comprising 50% Tenax® and 50% Carbotrap (Markes International Limited). The tubes were spiked with 1μl of internal standard d8-toluene in methanol by injection onto the front of the tube using a micro syringe and by then pumping nitrogen through the tubes for 30 seconds to get the standard onto the sorbent. This is the standard technique recommended by Markes International.

Chromatographic analyses were performed using an Agilent 6890/5973 GC-MS system equipped with a Markes TD autosampler, and Markes UNITY thermal desorber. The tubes underwent a pre-purge of 1.0 minute, followed by desorption at 260 °C for 3.0 minutes. The trap temperature was set at -7 °C and the actual trap desorption occurred at 300 °C for 3.0 minutes. The volatiles of interest were separated using a Restek column (60 m × 0.32 mm, film thickness 1.8 μm) working in a constant flow mode (helium at 30.8 ml min^{-1}). The column temperature program involved an initial increase from 35 °C to 60 °C at a rate of 11 °C min^{-1}, followed by a rate of 20 °C min^{-1} up to 220 °C, and a constant temperature of 220 °C for 10 minutes. The mass spectrometer was operated in a SCAN mode with an associated *m/z* range set from 33.0 to 260.0. The quadrupole, ion source, and transfer line temperature were kept at 150 °C, 230 °C and 230 °C, respectively.

2.6 Data processing

Prior to data analysis, the counts per second acquired by SIFT-MS were normalised (ncps) against the counts per second of the H_3O^+ (*m/z* 19) precursor ion. A high counts per second ($\leq 10^7$ cps) for H_3O^+ at *m/z* 19 occurs using PTR-MS, therefore detector saturation follows. For this reason, the isotope of oxygen, ^{18}O, is commonly used i.e. the, count rates at *m/z* 21 were measured to assess the counts per second of H_3O^+. PTR-MS signals were normalised (ncps) to a H_3O^+ signal of one million counts per second. The contribution of fragment ions and hydronium water-cluster ions was taken into

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account in the determination of VOC concentration via SIFT-MS and PTR-MS. Laboratory background air (SIFT laboratory and PTR-MS laboratory) was also analysed.

Using the internal standard approach via GC-MS, the determination of VOC concentration expressed in ng l^{-1} was achieved by means of the following equation:

$$C = \frac{abundance\ (\%)_{VOC}}{abundance\ (\%)_{d8-toluene}} \times 50\ ng\ \times \frac{1000\ ml}{100\ ml\ min^{-1} \times 5\ min\ \times 1\ L} \qquad (3)$$

where, the VOC concentration (C) is expressed in ng l^{-1} and the concentration expressed in ppbv was calculated; relative abundances of VOC and d8-toluene are expressed in percentage (%); 50 ng represents the mass of d8-toluene used to prepare the standard; with representative VOCs being pumped into sorbent tubes for 5 minutes at a constant flow of 100 ml min^{-1}. Typically, deuterated standards are used but in the case of biomarker discovery, is impossible to add into the tubes with deuterated standards of all possible compounds, so often just one or two internal standards are used. However a problem that arises with this technique is that each compound has a different affinity for the sorbent so the deuterated standard may not be appropriate for all possible VOC biomarkers. GC-MS data analysis was performed through the aid of AMDIS (Automated Mass Spectral Deconvolution and Identification System) software, and followed by reliable identification of compounds using the NIST (National Institute of Standards and Technology) library.

For SIFT-MS and PTR-MS, the signal (ncps) was plotted against the concentration (ppbv) and the sensitivity was withdrawn. For TD-GC-MS the plots are illustrated, i.e. the area of the analytes relative to the area of the internal standard against the concentration in the sample. Concentrations were rounded up to the unit and further used.

3. Results and discussion

3.1 Product ions and branching ratios in SIFT-MS and PTR-MS analysis

All of the analytes have higher proton affinities than H_2O (691.0 kJ mol^{-1}) [23], and so rapid proton transfer occurs in each case in SIFT-MS and PTR-MS. In this study proton transfer from H_3O^+ to VOCs has been investigated with the product ions and their associated branching ratios being identified (Table 3).

Our results are in agreement with earlier measurements, where methanol has been thoroughly studied using SIFT-MS and PTR-MS [27-28]. Saturated aldehyde reactions with H_3O^+ have been previously studied by SIFT-MS, where only non-dissociative proton transfer is seen (*m/z* 45) for acetaldehyde reactions [29-30]. However ion chemistry studies on H_3O^+–acetaldehyde reactions by PTR-MS have not yet been exhaustively studied. Our results were delivered at *E/N* of 160 Td, where non-dissociative proton transfer is seen, yielding *m/z* 45 as the major product ion, with additional clustering of the protonated ion to produce ROH$^+$·H_2O at *m/z* 63. Reaction of ethanol through SIFT-MS yields the protonated ion ROH$_2^+$ at *m/z* 47 and an additional clustering of the protonated ethanol monomer species to H_2O to produce ROH$_2^+$(H_2O)$_{1,2}$ [27]. Ethanol reaction in PTR-MS, using an *E/N* of 92 Td yields ROH$_2^+$ at *m/z* 47 as the major product ion, ROH$_2^+$·H_2O at *m/z* 65 and *m/z* 45 (C$_2$H$_5$O$^+$) corresponding to a loss of H_2 [28]. Our findings confirmed that acetone reacts by non-dissociative proton transfer to produce a single protonated product ion ROH$^+$ either by SIFT-MS and PTR-MS [29, 31]. The branching ratios for the isomers 1-propanol and 2-propanol have been thoroughly studied by Warneke and co-workers who determined that the proton transfer between H_3O^+ and a VOC is

non-dissociative [11], where the loss of water from the protonated alcohol is predominant and, consequently, breaking up to m/z 43 ($C_3H_7^+$) and yielding in addition the product ion ROH_2^+ at m/z 61 [27-28].

3.2 Theoretical prediction of reaction rate coefficients

A vast number of rate coefficients of VOCs with H_3O^+ at thermal energy have been experimentally determined using SIFT-MS with a reported accuracy better than 10% [27, 29, 32-34]. The rate coefficients have been calculated using the parameterised trajectory formulation of Su and Chesnavich [35] within an estimated accuracy ± 10%. The rate coefficients at thermal conditions have been previously reported in the literature [27, 29].

In contrast the kinetics of ion-molecule reactions of PTR-MS is not well-defined, literature data on reaction rate coefficients is scarce, and can be sensitive to *E/N* [11, 36-37]. A standard value (2×10^{-9} cm^3 s^{-1}) for the proton transfer rate coefficient (k_{cap}) is often used to estimate trace-gas concentrations. Quantification is directly dependent on k_{cap}, which means that using the same proton transfer rate coefficient for different ion-molecule reactions may introduce a significant uncertainty to the quantification.

Proton transfer reactions between H_3O^+ and VOCs in both SIFT-MS and PTR-MS occur efficiently if the proton affinity of the acceptor molecule exceeds the proton affinity of the donor (H_2O), thus such reactions are exothermic. Exothermic proton transfer reactions in the gas-phase tend to be fast ($k \geq 10^{-9}$ cm^3 s^{-1}) and usually proceed at the collisional rate [38-39].

The estimation of rate coefficients of exothermic ion-molecule reactions is possible, if the polarizability and the dipole moment of the reactant molecule are known. Therefore, ion-neutral molecule collision theories have been applied, and the reaction rate coefficients were calculated according to the detailed description given by Cappellin and co-workers [37].

Table 4 shows the theoretical prediction of proton transfer rate coefficients, k_{cap} (T_{rot},KE_{cm}), for the proton transfer reactions occurring in the drift tube of PTR-MS at 373 K, calculated via Su and Chesnavich trajectory theory [40]. For comparison, reaction rate coefficients were calculated via the Langevin theory [41], and Average Dipole Orientation (ADO) theory [42]. These rate coefficients k_{cap} (T_{rot},KE_{cm}) are later used in the quantitative determination of VOC concentration via PTR-MS.

Ion-molecule reactions in PTR-MS proceed with energies larger than thermal energy due to the existence of a homogenous electrical field. The kinetics of ion-molecule reactions in PTR-MS is controlled not only by pressure and temperature in the drift tube but also by the electric field strength yielding further ion-molecule collisions than those at 300 K for SIFT-MS [44]. Increasing the electric field strength on PTR-MS or decreasing the pressure or temperature of the drift tube in turn increases the drift velocity and, consequently, the kinetic energy of the ions. The kinetic energy of the ions is higher than the drift-tube temperature as a result of the selective heating of the ions by the electric field. Therefore, this additional energy applied by the electric field should be taken into account. This means that is necessary to consider the centre-of-mass kinetic energy (KE_{cm}) for a collision between an ion and the neutral molecule in the determination of reaction rate coefficients in PTR-MS [45-46]. Rate constants, k_{cap} (T_{rot},KE_{cm}) were calculated according to the detailed description given in Su's trajectory calculations [40]. While the accuracy of the model to determine the rate coefficient is improved by utilising $k_{cap}(T_{rot},KE_{cm})$, the uncertainty is also increased compared to simpler models.

3.3 Quantitative determination of VOC concentrations

3.3.1 Individual headspaces

Quantification of VOC concentrations without calibration may be accomplished if proton transfer reaction rate coefficients are known for example Su's parameterised kinetic energy dependence of ion-molecule reaction rate coefficients k_{cap} (T_{rot}, KE_{cm}) can be used to determine the VOC concentration. VOC concentrations were derived in parts-per-billion by volume (ppbv) according to the detailed description given by Cappellin and co-workers [13]. Table 5 presents a comparison between the techniques used for 5 ppm in the headspace. Concentrations were corrected for the ambient air temperature in the laboratory. The compound-dependent sensitivity of SIFT-MS and PTR-MS is expressed in ncps/ppbv and is listed in Table 5.

The contribution of fragment ions and hydronium water-cluster ions was taken into account in the determination of VOC concentration via SIFT-MS and PTR-MS. In gas samples with higher humidity, the number of water-cluster ions is significantly enhanced, and these may play a role as a reagent ion.

Calibration curves (Figure 1 and Figure 2) for the six VOCs are represented hereafter. The linearity of the response was verified for all compounds.

Under standard operating conditions and for most VOCs, *E/N* is in the range 120–130 Td. This has recently become the guideline for numerous experiments. Nevertheless, the effects on the underlying ion-chemistry must be carefully considered depending on the *E/N* ratio. The purpose of this paper was not to study product ion distributions over *E/N* but our findings indicated that quantification via PTR-MS is sensitive to alterations in the reduced electric field (i.e. changes in the *E/N* ratio) and significantly influences the quantification of compounds in the gas-phase, as shown in figure 3.

For most of the molecules used in this study product ion distributions as a function of *E/N* have been widely described in literature [28]. With the increase in the *E/N* ratio, the signal drops significantly along with the decrease of the reaction time, which in turn promotes the fragmentation channels described previously.

3.3.2 TD-GC-MS results

The VOCs have been trapped in stainless-steel TD sorbent tubes and further desorbed into the GC column. The MS detector was setup to scan from *m/z* 33.0 to *m/z* 260.0, therefore, methanol was not detected through this specific GC-MS method. Sorbent tubes used in VOC analysis are typically chosen to capture a range of VOCs, however, some very low molecular mass VOCs do not adsorb consistently to typical sorbents chosen for this purpose. The results here show that although acetaldehyde and ethanol could be trapped and detected, they were not trapped consistently according to concentration. This highlights the importance of performing calibration and standardisation tests on all techniques used to analyse multiple analytes.

Calibration functions using the internal standard procedure for 1-propanol, 2-propanol and acetone at physiologically representative concentrations are represented in figure 4.

The internal standard calibration curves plots the area of the analytes relative to the area of the internal standard against the concentration in the sample. The parameter determined relative to the internal standard is thus independent of deviations in the injection volume and possible variations in the performance of the detector [8]. These calibrations functions are specific for a sampling flow of 100 ml min^{-1} for 5 minutes, and 50 ng of internal standard d8-toluene was used.

3.3.3 VOC mixtures

A volatile mixture is usually present in biological samples, which may respond differently once combined, the stability in the gas-phase of VOCs mixtures has been evaluated by using TD-GC-MS as explained in section 2.4.

Solutions containing acetone, 1-propanol, 2-propanol, ethanol, acetaldehyde and methanol were prepared in order to give headspace concentrations of these compounds of 10 ppm, 5 ppm, 1 ppm and 0.1 ppm. Internal standard calibration curves for the mixtures are given in figure 5, where a sampling flow of 100 ml min^{-1} for 5 minutes was used and 50 ng of internal standard d8-toluene.

Peaks elute along the GC column according to their affinity for the stationary phase of the column. Polar compounds interact weakly with low polarity stationary phases, as commonly used in VOCs analysis, and consequently, short retention times follow. It should be noted that competitive binding may occur and the significance of this for an accurate quantification is not yet fully understood. At a specific gas-phase concentration (i.e. 0.1 ppm, 1 ppm, 5ppm, and 10 ppm), the peak areas observed for the mixtures are significantly lower than for the individual solutions (figure 6 (a), (b), (c)). This could possibly be due to competitive binding within the column. Among all the VOCs separated in the column, 2-propanol binds most strongly to the stationary phase due to its highest relative polarity and eluting later on at 7.1 minutes (figure 6 (d)).

4. Conclusions

This study has shown the potential for using a simple mix of standards generated using Henry's law data to evaluate the accuracy of different analytical instruments in quantifying VOCs. Many studies have been carried out analysing volatile metabolites but often there is little agreement between the levels of some compounds. By this inexpensive and simple way of producing calibration standards, a comparison between techniques may easily be made. For instance, this study has shown that while SIFT-MS and PTR-MS may be able to detect ethanol and acetaldehyde simply and accurately, a typical TD-GC-MS technique used in VOC biomarker discovery is poor at quantification of smaller compounds due to the need to carefully pick sorbents to cover the range. The accuracy of the measurements yielded errors of $\pm$ 20%, $\pm$ 50%, and $\pm$ 20% determined via SIFT-MS, PTR-MS and TD-GC-MS, respectively (Table 5). A comparison between the three analytical techniques indicated differences in acetone concentrations less than 30% in contrast to the published literature between SIFT-MS/TD-GC-MS where concentration differences greater than 30% were reported [47]. While for the isomers 1-propanol and 2-propanol greater differences in concentration were observed. Differences in concentrations have shown to be greater than 60% between either PTR-MS/TD-GC-MS or SIFT-MS/PTR-MS, however, a comparison between SIFT-MS/TD-GC-MS demonstrated a far better accuracy (concentration difference inferior to 26%) in the detection of the isomers. The three

techniques are complementary although some situations (e.g. overlapping product ions) require the use of one detection technique in particular.

The results of the present study of the reactions of H_3O^+ with six VOCs comprising several alcohols, one ketone and one aldehyde, indicate that most of the reactions result in multiple products ions, and the abundance and stability of these ions strongly depends on the *E/N* ratio used. Importantly, the reaction rate coefficients for the reactions between H_3O^+ and VOC need to be determined under the actual working settings in order to obtain reliable quantification. Product ions and branching ratios were determined at particular working conditions, and subsequently, quantitative determination of VOC concentrations evaluated. Calibration curves determined using SIFT-MS, PTR-MS and TD-GC-MS are given within the range 10^1-10^3 ppbv.

In this study we show the approach taken of using standard headspaces enables a proper comparison to be made between the three analytical techniques and enables these techniques to be tested for their accuracy and reproducibility. This study also provides an estimate of how accurately rate coefficients can be determined in SIFT-MS and PTR-MS. This study demonstrates the feasibility of testing the instruments and to find out whether these give consistent results amongst each other. This is a very important feature required particularly for the accurate identification and quantification of chemical fingerprints in the gas-phase for its use in disease diagnosis.

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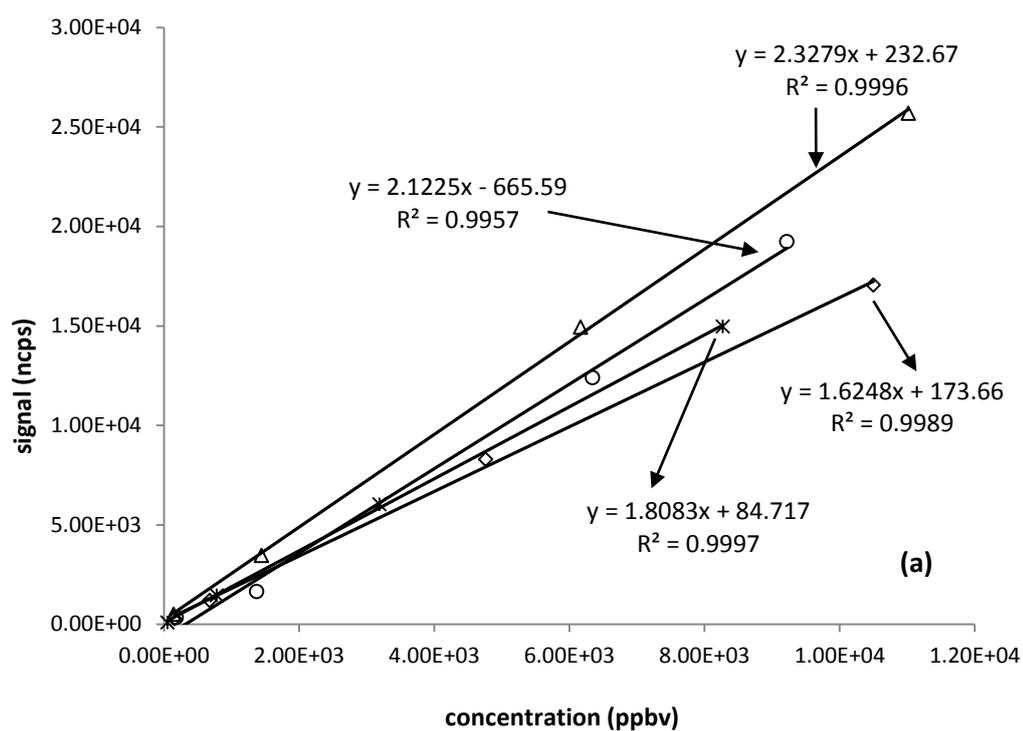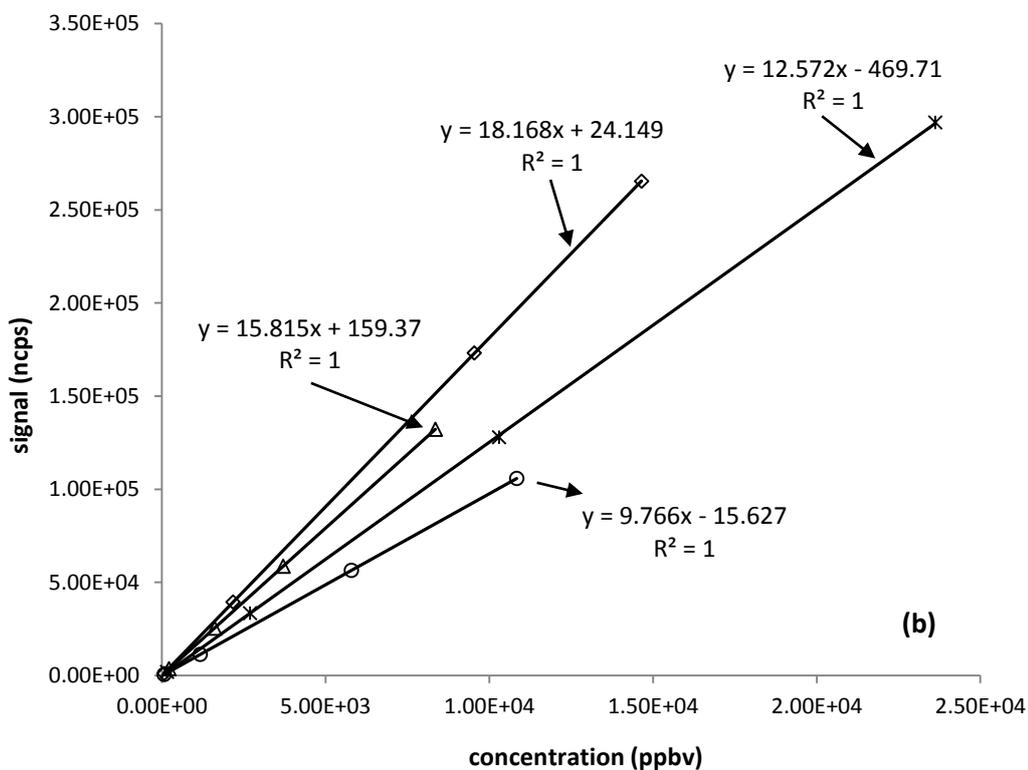
Figure 1. Calibration curves for 1-propanol, 2-propanol, ethanol and methanol at physiologically representative concentrations; data acquired using SIFT-MS **(a)** and PTR-MS **(b)**.
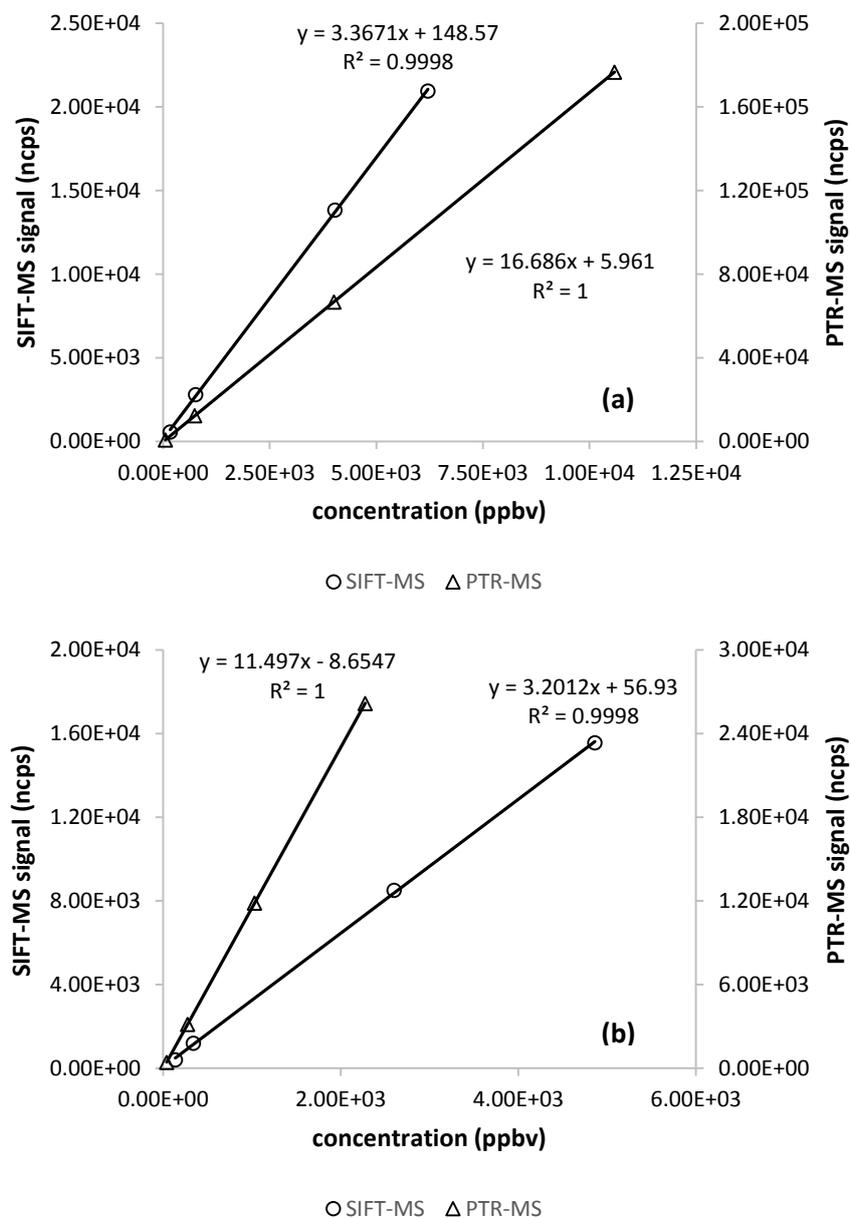
Figure 2. Calibration plot for acetone **(a)** and acetaldehyde **(b)** at physiologically representative concentrations; data acquired using SIFT-MS and PTR-MS.

(a)

(b)

(c)
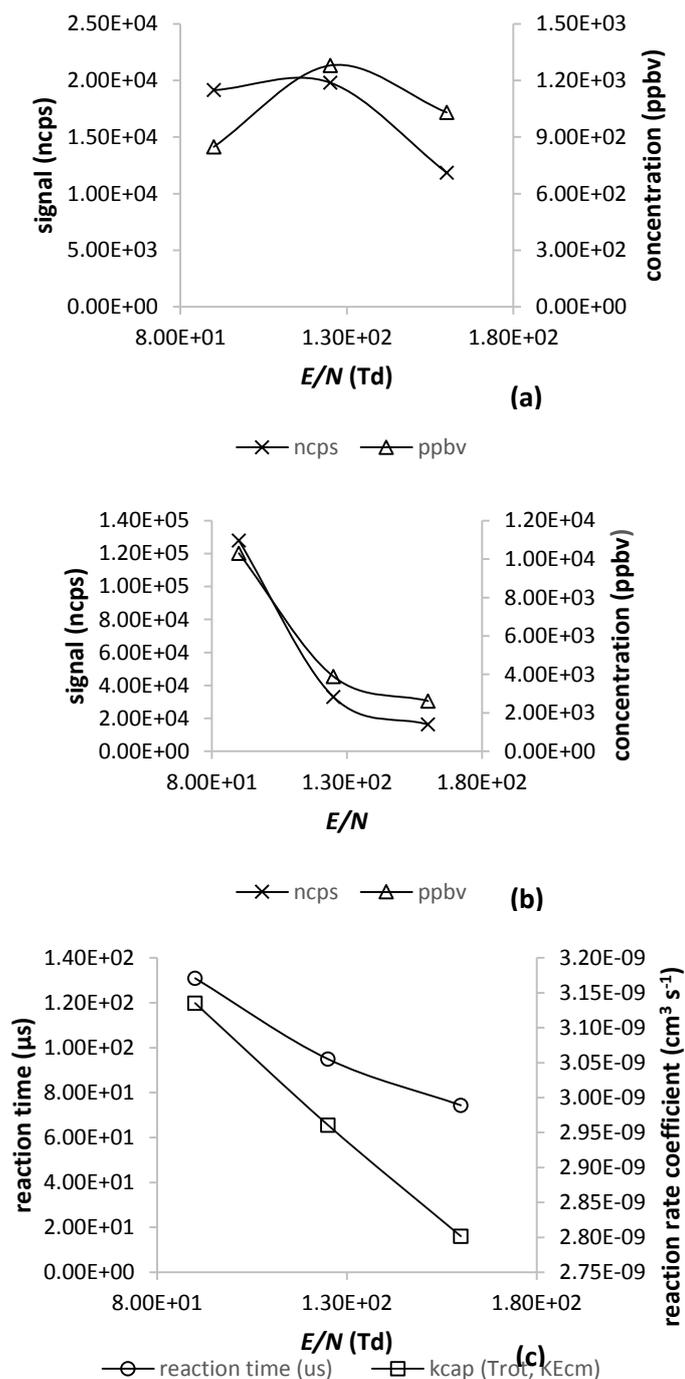
Figure 3. (a) Concentration of acetaldehyde in ppbv and **(b)** 2-propanol in ppbv, calibrated to 5 ppm in the gas-phase, and normalised counts per second (ncps) as a function of reduced electric field strength (E/N = 90, 125, 160); **(c)** Acetaldehyde-H_3O^+ reaction time and reaction rate coefficient as a function of E/N = 90, 125, 160.
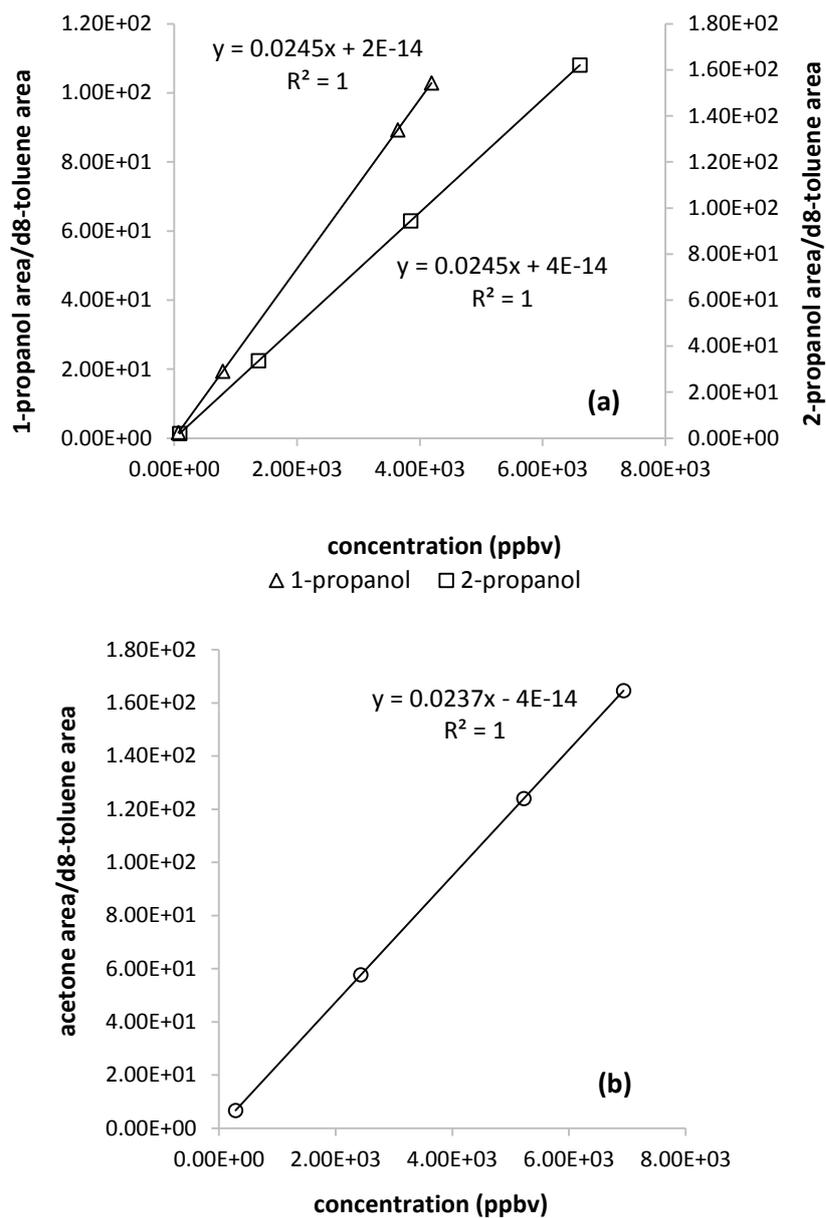
Figure 4. Calibration functions using the internal standard procedure for 1-propanol, 2-propanol (**a**) and acetone (**b**); data acquired using TD-GC-MS.
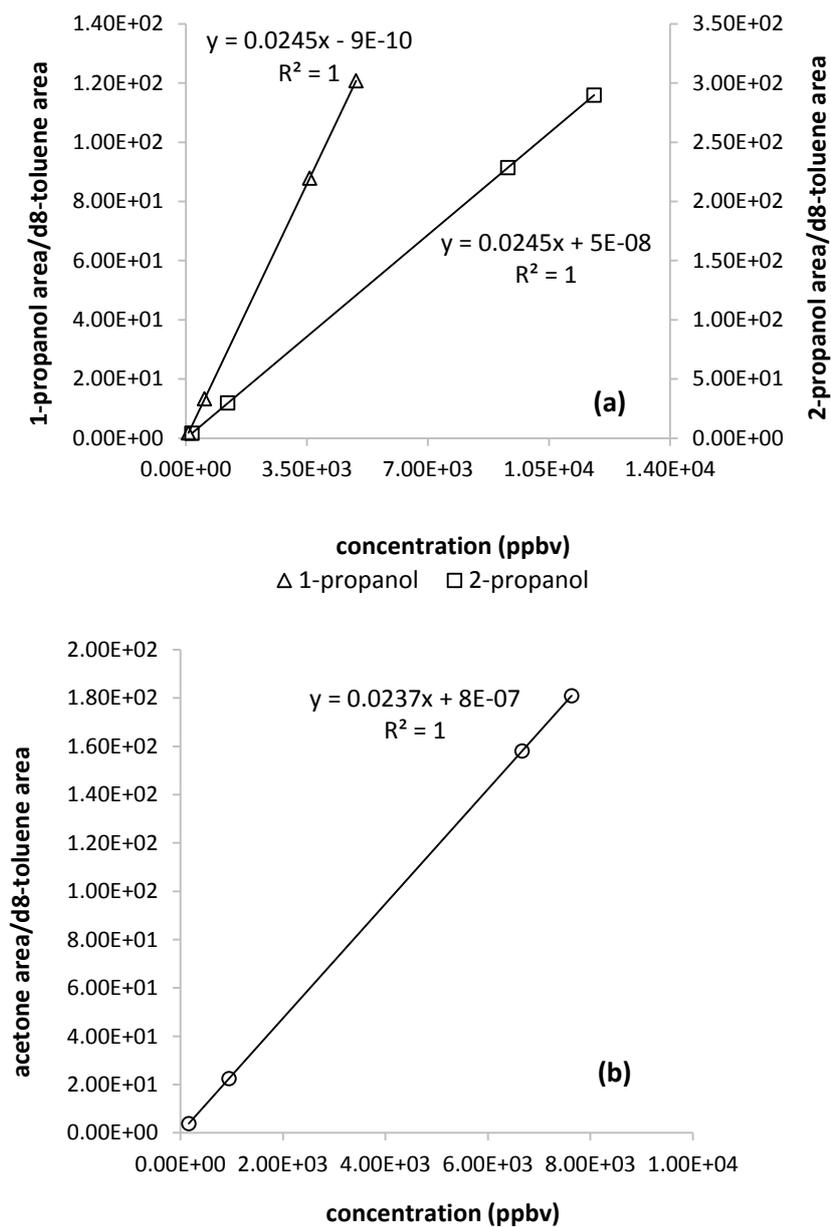
Figure 5. Calibration functions using the internal standard procedure for 1-propanol and 2-propanol within a mixture of VOCs **(a)** and acetone **(b)**; data acquired using TD-GC-MS.

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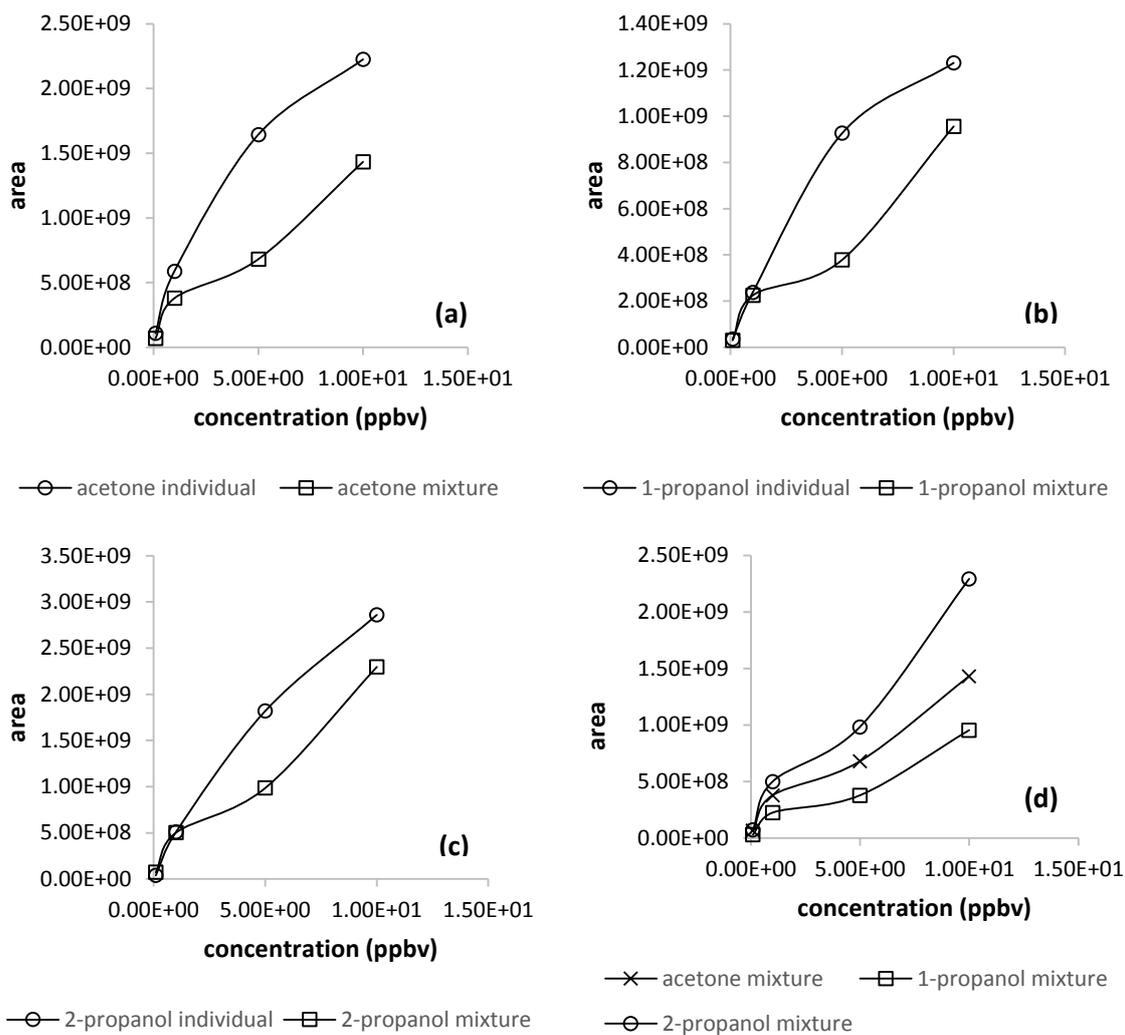
Figure 6. Comparison of the peaks areas observed in chromatograms acquired using TD-GC-MS for individual calibration solutions, and peak areas acquired for a VOC mixture containing the six VOCs analysed **(a)** acetone**, (b)** 1-propanol**,** and **(c)** 2-propanol; **(d)** comparison of peak areas within the VOC mixtures at gas-phase concentrations of 0.1 ppm, 1 ppm, 5ppm, and 10 ppm.

Table 1. Henry's law constants at 298 K ($k°_H$), $\Delta_{sol}H/R$ values in K and the derived Henry's law constants (k_H) at 293 K for acetone, ethanol, methanol, 1-propanol, 2-propanol, acetaldehyde in aqueous solution. Mean values are given for $k°_H$ and $\Delta_{sol}H/R$.

|	$k°_H$ [(mol dm^{-3}) atm^{-1}] 298 K [a]	$\Delta_{sol}H/R$ [K] [a]	k_H [(mol dm^{-3}) atm^{-1}] 293 K
Acetone	3.00×10^1	4.60×10^3	3.90×10^1
Ethanol	1.84×10^2	6.50×10^3	2.68×10^2
Methanol	2.04×10^2	5.40×10^3	2.78×10^2
1-propanol	1.38×10^2	7.50×10^3	2.12×10^2
2-propanol	1.27×10^2	7.50×10^3	1.95×10^2
Acetaldehyde	1.29×10^1	5.37×10^3	1.75×10^1

[a] Reference [23-24].

Table 2. Ionization conditions in the drift tube of PTR-MS

VOC	*Drift voltage* (V)	*Drift pressure* (mbar)	*E/N* (Td)
Acetone	288	1.30	125
Ethanol	230	1.31	99
Methanol	305	1.37	125
1-propanol	230	1.38	94
2-propanol	209	1.31	90
Acetaldehyde	370	1.31	160

Table 3. Comparison of the product ions identified by SIFT-MS and PTR-MS and their associated ion branching ratios (percentage in parentheses), respectively, calibrated for 5 ppm in the headspace, for a series of saturated alcohols (ROH), acetone (RO) and acetaldehyde (RO). Errors in the branching ratios are estimated to be less than 10%.

VOC	Molecular formula (MW)	SIFT-MS Product ions and ion branching ratios (%)	PTR-MS Product ions and ion branching ratios (%)
Methanol	CH_3OH (32)	33 (41) ROH_2^+ 51 (28) $ROH_2^+ \cdot H_2O$ 69 (31) $ROH_2^+ \cdot (H_2O)_2$	33 (96) ROH_2^+ 51 (4) $ROH_2^+ \cdot H_2O$
Acetaldehyde	C_2H_4O (44)	45 (41) ROH^+ 63 (47) $ROH^+ \cdot H_2O$ 81 (12) $ROH^+ \cdot (H_2O)_2$	45 (54) ROH^+ 63 (46) $ROH^+ \cdot H_2O$
Ethanol	C_2H_5OH (46)	47 (15) ROH_2^+ 65 (45) $ROH_2^+ \cdot H_2O$ 83 (40) $ROH_2^+ \cdot (H_2O)_2$	45 (1) $[ROH-H_2]H^+$ 47 (51) ROH_2^+ 65 (48) $ROH_2^+ \cdot H_2O$
Acetone	C_3H_6O (58)	59 (39) ROH^+ 77 (61) $ROH^+ \cdot H_2O$	59 (100) ROH^+
1-Propanol	C_3H_7OH (60)	43 (70) R^+ 61 (2) ROH_2^+ 79 (6) $ROH_2^+ \cdot H_2O$ 97 (22) $ROH_2^+ \cdot (H_2O)_2$	43 (77) R^+ 61 (6) ROH_2^+ 79 (17) $ROH_2^+ \cdot H_2O$
2-Propanol	C_3H_7OH (60)	43 (54) R^+ 61 (5) ROH_2^+ 79 (29) $ROH_2^+ \cdot H_2O$ 97 (12) $ROH_2^+ \cdot (H_2O)_2$	43 (68) R^+ 59 (1) $[ROH-H_2]H^+$ 61 (12) ROH_2^+ 79 (19) $ROH_2^+ \cdot H_2O$

Table 4. Proton transfer reaction rate coefficients k_{cap} (T_{rot}, KE_{cm}) (10^{-9} cm^3 s^{-1}) between hydronium ion (H$_3$O$^+$) and selected VOCs at 373 K, T_{rot} is taken as the drift tube temperature. For comparison, reaction rate coefficients k_L, k_{ADO}, and k_{cap} (T_{eff}) are also reported and expressed in 10^{-9} cm^3 s^{-1}. Also given are their polarizabilities, α, expressed in units of 10^{-30} m^3 and their permanent dipole moment, μ, in Debye, D.

VOC	α (10^{-30} m^3) [a]	μ (D) [a]	k_L (10^{-9} cm^3 s^{-1})	k_{ADO} (10^{-9} cm^3 s^{-1})	k_{cap} (T_{eff}) (10^{-9} cm^3 s^{-1})	k_{cap} (T_{rot},KE_{cm}) (10^{-9} cm^3 s^{-1})
Acetone	6.40	2.88	1.57	3.10	2.24	3.10
Ethanol	5.26	1.69	1.46	2.14	1.89	2.36
Methanol	3.29	1.70	1.23	2.13	1.66	2.21
1-propanol	6.74	1.58	1.60	2.21	1.96	2.33
2-propanol	6.97	1.58	1.63	2.24	1.99	2.37
Acetaldehyde	4.59	2.75	1.38	2.97	1.93	2.80

[a] Reference [43].

Table 5. Determination of VOC concentrations calibrated to 5 ppm in the headspace (i.e. sampling bags containing solutions calibrated to 5 ppm in the headspace, according to the details of sample preparation given in 2.1) and a comparison between the mass spectrometric techniques used and TD-GC-MS; SIFT-MS and PTR-MS sensitivity in ncps/ppbv within the range 10^1-10^3 ppbv.

VOC	Concentration (ppbv)			Retention time (min)	Sensitivity (ncps/ppbv)	
	SIFT-MS [a]	PTR-MS [b]	TD-GC-MS [c]		SIFT-MS [a]	PTR-MS [b]
Acetone	4027	4004	5230	6.6	3.4	16.7
Ethanol	6167	3700	--	6.1	2.4	15.8
Methanol	6347	5782	--	4.2	2.0	9.76
1-propanol	4760	9536	3638	9.2	1.7	18.2
2-propanol	3189	10294	3848	7.1	1.9	12.4
Acetaldehyde	2600	1030	--	4.1	3.3	11.5

[a] Errors of ±20%, [b] ±50%, and [c] ±20% are assigned to the quantification via SIFT-MS, PTR-MS and TD-GC-MS, respectively. These were determined using the concentrations obtained via SIFT-MS, PTR-MS and TD-GC-MS when compared to the concentrations expected in the headspace.