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Full Length Article

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

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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 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.

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 standardisation 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.

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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:

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

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].

$$\frac{dlnk_H}{d\left(\frac{1}{T}\right)} = \frac{-\Delta_{sol}H}{R} \quad (2)$$

here, k°_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°_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 l 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 l 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