Control and calibration of atmospheric pressure chemical ionisation processes in ion mobility spectrometry using piezoelectric dispensers

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Control and Calibration of Atmospheric Pressure Chemical Ionisation Processes in Ion Mobility Spectrometry Using Piezoelectric Dispensers

A thesis submitted to Loughborough University for the degree of Doctor of Philosophy

Victor Moll

2011
Abstract

If the analyses of trace components in complex organic samples are to be optimised, then these compounds must be isolated either physically or chemically from surrounding matrices. Ion mobility spectrometry (IMS) is an analytical technique used worldwide for the detection of on-site trace compounds. The technique can be optimised to isolate the target species from complex matrices through both physical separation, based on the mobility of the analyte ions at ambient pressure, and chemical discrimination through preferential ionisation of the target. Optimisation of the latter is commonly achieved through doping the spectrometer with a selective reagent gas, termed a dopant. The chemical processes required to optimise the responses of target analytes are dependent on the identity and concentration of the dopant. As such, a variety of dopants have been successfully implemented in ion mobility spectrometers. The technology for the deliverance of dopants in IMS is commonly through permeation sources, which provide a stable chemical environment in the ion mobility cell. Although relatively inexpensive and durable, these devices are difficult to change and generally deliver a single dopant concentration. As a result, only one type of chemistry is possible and the responses cannot be optimised for a range of analytical applications. Such limitations become increasingly significant when IMS is hyphenated to a chromatograph where a range of different dopant conditions may be sought over the course of a chromatographic run.

This thesis sought to overcome these limitations through the development and implementation of piezoelectric dispensers, interfaced directly to the transport gas regions of IMS cells. The study demonstrates for the first time the ability to use piezoelectric dispensing as a dopant introduction methodology in IMS for controlling and calibrating a range of dopant chemistries. 2-butanol, acetone, dichloromethane, 1-chlorohexane, 4-heptanone and 1-bromohexane were the candidate dopants chosen for the studies, covering a wide range of physical and chemical properties. The novel technology was used to dispense the target dopants into IMS cells at concentration ranges over three orders of magnitude. Dopant chemistries were achieved within three seconds from the point of dispensing, administered in drop-on-demand formats, and could be delivered either transiently or at steady-state concentrations. The concept was validated through integrated spectral dopant responses. In transient control, dynamic linear relationships of $R^2 = 0.991 – 0.998$ were achieved between dispensed dopant mass and peak area. Under continuous operation, the RSD of the dopant level was $< 18\%$ for all dopants. Clear out times for dopant responses were in the order of 3–5 seconds, indicating negligible hysteresis effects.

The study also proved the concept of controlling monomer and dimer ion chemistries from 2-butanol actuations when interfaced to a differential mobility spectrometer at mass fluxes between 21 – 1230 ng m$^{-3}$, and the simultaneous control of dopants in negative and positive ionisation modes to RSDs <10%. This thesis describes the techniques used to optimise the piezoelectric dispensing of the full dopant range, as well as the full design protocols required to interface to mobility spectrometers. The outcomes from these studies provide a realisation for piezoelectric dispensers as a future mainstream dopant introduction technique for the analysis of complex samples.

Keywords: Ion mobility spectrometry, piezoelectric dispensing, calibration, dopants, atmospheric pressure chemical ionisation, volatile organic compounds.
CERTIFICATE OF ORIGINALITY

This is to certify that I am responsible for the work submitted in this thesis, that the original work is my own except as specified in acknowledgments or in footnotes, and that neither the thesis nor the original work contained therein has been submitted to this or any other institution for a degree.

Victor Moll

...................................................... (Signed)

22/11/2011

...................................................... (Date)
List of Publications

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Dedication

This thesis is dedicated to the memory of Victor Moll Snr. If I can accomplish half as much in my life as you did in yours, I will have achieved an awful lot!
Acknowledgements

I am highly indebted to the enthusiasm, commitment, and above all, friendship of Professor Paul Thomas, without whom this work would never have started, let alone reached a successful conclusion. His wisdom and contagious drive for excellence have enabled me to achieve what, at many times, I didn’t think was possible.

My sincerest gratitude goes out to all my colleagues at Loughborough for making my time there as happy and fulfilling as I have ever known. In particular to Big Vee and Jim for their dedication and for putting up with all my misdemeanours, of which there were many! I owe special thanks also to my dear friend Cris, who has been with me throughout this journey, and will always be an integral part of my life. To everyone who has given me support, laughter and happiness along the way: Dorota, Nikki, Lauren, Pareen, Mark, Emma, Gavin, Helen, Matt, Rob, Vikki, Shuo, Ran(ital), Neil, Caitlan, Corrinne, Andreea, Aadi, Sultan…I love you all!

External collaboration and support was crucial to the successful conclusion of this project, and I wish to thank John Hogg Technical Solutions, Shell Global Solutions and the Department of Trade and Industry for the funding and technical input that they provided throughout the work.

For her support, energy and passion, I owe much of what I have accomplished to my partner, Eva. We have shared many extremes of emotion during the past three years, but she has always been there to listen and advise me; not least at times where I could see very little light.

My defining gratitude and love is towards my family, who have supported me through thick and thin and given me every opportunity that a person could wish for. It has been a long road, but I hope that I have made you as proud as I am of you.
“Your imagination is your preview of life’s coming attractions”

Albert Einstein
Abbreviations and Definitions

Abbreviations

APCI    Atmospheric pressure chemical ionisation
CCD    Central composite design
DMS    Differential mobility spectrometry
DOD    Drop-on-demand, as applied to piezoelectric dispensing
EA    Electron affinity (kJ mol$^{-1}$)
ESI    Electrospray ionisation
GC    Gas chromatography
IMS    Ion mobility spectrometry
LDR    Linear dynamic range
MS    Mass spectrometry
OPC    Organophosphorous compound
PA    Proton affinity (kJ mol$^{-1}$)
PZX    Piezoelectric
RIP    Reactant ion peak
RSD    Relative standard deviation
TAG    Test atmosphere generator
VOC    Volatile organic compounds

Definitions of symbols

$E/N$    Ratio of applied electric field to number density of the drift gas (Td)
$K$  Ion mobility coefficient (cm$^2$ V$^{-1}$ s$^{-1}$)

$K_o$  Reduced ion mobility (cm$^2$ V$^{-1}$ s$^{-1}$)

$V_{dr}$  Ion drift velocity (cm s$^{-1}$)

$k$  Boltzmann constant ($1.38 \times 10^{23}$ J kg$^{-1}$)

$e$  Ion charge state

$\Omega$  Collisional cross section of ion

$V_c$  Compensation voltage in DMS (V)

$RF$  Dispersion voltage in DMS (V)

$E_c$  Compensation field in DMS (V cm$^{-1}$)

$CF$  Pre-concentration factor in sampling

$y_d$  Average droplet volume (pL)

$V_d$  Dwell voltage in bipolar waveform (V)

$t_d$  Dwell time in bipolar waveform (µs)

$V_e$  Echo voltage in bipolar waveform (V)

$t_e$  Echo time in bipolar waveform (µs)

$t_r$  Rise time in bipolar waveform (µs)

$t_f$  Fall time in bipolar waveform (µs)

$t_{fr}$  Final rise time in bipolar waveform (µs)

$p\%$  Relative droplet precision

$\omega$  Bipolar waveform frequency (Hz)

$T_r$  Reservoir temperature at PZX syringe (°C)

$Q$  Mass flux of dopant (ng min$^{-1}$)

$i_g$  Concentration of dopant vapour in glass liner (µg m$^{-3}$)

$[i_{CELL}]$  Concentration of dopant vapour entering the IMS cell (µg m$^{-3}$)

$M_i$  Dispensed mass per droplet (ng)

$F_1$  Compressed inlet flow rate to PZX interface (cm$^3$ min$^{-1}$)

$F_2$  Exhaust flow rate to PZX interface (cm$^3$ min$^{-1}$)

$F_3$  Split flow rate to PZX interface (cm$^3$ min$^{-1}$)

$F_4$  Flow rate exiting the capillary at the PZX interface (cm$^3$ min$^{-1}$)

$F_5$  Jet-pump inlet flow rate (cm$^3$ min$^{-1}$)
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Chapter 1

Introduction

1.1 Improving field analyses of complex samples

Consider the analysis of a complex organic sample such as that demonstrated in Figure 1.1; diesel taken from a motor vehicle in Karachi, Pakistan. Present within the 386 integrated peaks identified in the sample is solvent red 164, a dye added to the fuel in the ppm range, and used as an identifying marker for diesel in the Pakistani fuel market. Such dyes are tested on the roadside with ultra-violet spectrophotometry [1]. The method is cost-effective and the full test procedure takes in the order of 1-2 minutes. There is no necessity for complex and expensive analytical methods such as gas chromatography hyphenated to mass spectrometry (GC-MS) to enable red 164 to be detected and quantified in the field.
Figure 1.1 A gas chromatogram of a diesel sample obtained from Pakistan. I is the signal intensity and $t_r$, the retention time. The peak corresponding to solvent red 164 is represented by A. The sample was analysed by the author of this thesis, using headspace analysis as the sampling method and ion trap mass spectrometry for qualitative analysis of the peaks.

It is estimated that £350 million per year in customs and excise revenue is lost through the clandestine adulteration of fuels containing such markers in Northern Ireland alone [2]. The ease with which such dyes are isolated and identified facilitates not only their detection, but also their chemical duplication. Consequently it makes sense for companies and governments to develop more smart, secret and secure methods for labelling and detecting chemical markers in fuel samples [3,4]. Fuel labelling should provide detailed information about the fuel consignment ("smart"), be present at the ppb level ("secret") and be difficult to counterfeit ("secure"). Such a specification presents many complex analytical challenges. The conceptual framework objectives for such research would be:

- a series of markers present in fuels at concentrations detectable only by highly sensitive analytical instrumentation
- compatibility with fuel performance
- low toxicity
- chemical stability within a complex fuel matrix.
Finally, the instrumentation needed to accurately and precisely quantify the markers on time scales compatible with current methods must be available at an affordable price. The techniques must also be compatible with road-side testing.

Although sensitive and quantitative, the technique used to generate the chromatograph in Figure 1.1 would not meet such specifications. The run time is longer than an hour, GC-MS is not compatible for in-field analyses (due to high power requirements) and, the prerequisite for highly-trained personnel to operate such instrumentation all make the technique unfit for this purpose. The example of label detection in hydrocarbon fuels is just one of many current challenges affecting the chemical analysis of complex mixtures. The need for faster, more sensitive and target-specific detection methods in complicated environments is rapidly expanding, particularly with the perceived increased threat of terrorism following recent events impacting on a global scale [5]. Such challenges are not confined to screening fuel for labels; at the forefront of this field is the development of screening methods for the online detection of biomarkers in human disease in complex matrices such as saliva, skin and breath [6,7,8].

1.2 Ion mobility spectrometry for detecting trace components

The detection of a trace compound within a complex matrix requires prior knowledge of the chemistry of both the analyte and the sample matrix to enable its isolated form to be presented to the detector. This may be achieved either through the physical separation of the analyte, as is the case with chromatographic techniques, or through optimisation of the chemical processes that are associated with the transduction of the analyte. Ion mobility spectrometry (IMS) is a fieldable analytical technique, capable of exploiting both the chemical processes of a sample and its physical separation. Gaseous compounds within a sample are ionised in a reaction region inside the spectrometer cell and separated based upon the mobility of the generated ions as they pass through a drift cell under the influence of an applied electric field (see Section 2.3 and Figure 2.1). Both the ionisation and separation processes are compound dependent [9]. The utility of IMS as a fieldable technique stems from its:
- sensitivity
- ability to operate under ambient pressures (low power requirements)
- portability
- sampling times for analysis in the order of seconds [10].

Ion mobility spectrometers, Figure 1.2, are routinely employed in the field for the analysis of trace compounds at the ppb range in complex matrices such as ambient air. They are most commonly used for explosive and chemical weapons detection at airports, where high throughput analyses and low detection limits are the principal objectives [9].

![A photograph of a fieldable ion mobility spectrometer](image)

**Figure 1.2** A photograph of a fieldable ion mobility spectrometer, marketed under the name, chemical agent monitor (CAM) by Smiths Detection. The device uses a membrane inlet to sample gaseous atmospheric vapours, and a permeation source containing acetone to dope a carrier gas of air and control the ionisation chemistry at the reaction region of the cell.

If we return to our marker-in-fuel example, given in Figure 1.1, these benefits support IMS as being a potentially suitable technique for the characterisation of markers in fuels. If we consider, however, that hydrocarbon fuels possess multiple thousands of volatile organic compounds (VOCs), the ability of such instrumentation to detect a specific marker at the ppb range becomes all the more complicated[11]. This complication would be confounded further if multiple markers were required within
the fuel to enhance the “secure” aspect of fuel marking. In such situations, the mere separation of the target marker ion from all other matrix ions solely by ion mobility principles may not be sufficient. IMS may address this analytical requirement by manipulating the ionisation processes through the introduction of a reagent compound, termed a dopant, to the spectrometer. In the chemical agent monitor (CAM) shown in Figure 1.2, acetone is introduced as the dopant for optimising the ionisation processes. Ionisation mechanisms are discussed in detail in Section 2.5. Dopants simplify ion mobility spectra by suppressing the ionisation from interfering matrix components, and therefore enhance both the resolution and sensitivity of the target ion [12]. This makes IMS a particularly suitable technique for marker detection in fuels.

1.3 Limitations of current IMS dopant technologies

Ionisation processes in IMS are dependent upon the identity of the sample components and the supporting atmosphere inside the spectrometer. As a consequence, when optimising the detection of trace components in a complex matrix, dopant chemistry and concentration are fundamental considerations. If we once again refer to the example of labelling fuel markers at ppb levels inside the fuel matrix, it is apparent that the dopant and concentrations of dopant required to optimise the detection of these markers will be marker specific. In this case, multiple chemistries would be required to be delivered to the spectrometer, potentially at different times during the analysis stage, assuming that a pre-separation stage such as gas chromatograph is used.

Although dopants are regularly utilised in IMS analyses, and their effects well understood [9], current methods for dopant introduction do not possess the technology flexible enough for permitting the introduction of multiple dopants over concentration ranges of several orders of magnitude. Commonly, only one concentration of a single dopant is provided to the spectrometer in commercial systems [13,14]. The devices use permeation sources to provide dopant vapours to the spectrometer, which provide a stable atmosphere inside the spectrometer cell, but cannot be used to optimise the detection characteristics for a wide range of analytes. Permeation sources are also limited to compounds which provide sufficient vapour pressures to enable a change in the ambient atmosphere within the spectrometer. It is apparent that these methods would not be able to support the
analytical requirements necessitated from the example with fuel markers, particularly if the ionisation processes of multiple markers differed substantially. There is therefore a clear analytical need to develop technology that can overcome these limitations and increase the compatibility of IMS to detect multiple trace targets within complex matrices.

1.4 Potential for using piezoelectric dispensers in ion mobility systems

Piezoelectric (PZX) dispensers are routinely used to deliver drop-on-demand depositions of fluids in a variety of fields, including ink-jet printing, fuel injection and precision applications for drug delivery [15]. These devices dispense liquids at volumes as low as $10 \pm 0.1$ pL. They are able to do this by utilising the reverse piezoelectric effect (Section 2.6), where a high electrical potential is applied to a crystal lattice containing a finite quantity of fluid to spatially distort the lattice to $<1 \mu$m precision. PZX dispensers have been used recently in the field of chemical analysis to deliver precise quantities of liquid samples to gas chromatographs as a means for next-generation methods of sample introduction [16]. Although they have never been interfaced directly to IMS systems, PZX dispensers appear to be particularly applicable as a novel technology for dopant introduction. In addition to high dispensing precision, drop-on-demand dispensing of masses over several orders of magnitude can be generated from manipulation of the frequency of the applied waveform [17-18]. Further, the applicability of dopant responses that could be generated from PZX dispensers are not limited to dopant compounds that produce a sufficient vapour pressure at a given temperature, unlike permeation methods.

1.5 Research aims and objectives

This research tests the hypothesis that PZX dispensers can be interfaced to ion mobility spectrometers and used as a novel method for dopant introduction to overcome existing limitations with dopant technologies. The individual objectives for the study were:
- To design, develop and optimise an interface between a PZX dispenser and ion mobility spectrometer cells
- To optimise the PZX dispensing characteristics for a range of potential candidate dopants
- To prove the concept of using PZX dispensing to control and calibrate the chemical ionisation processes of dispensed dopants, using both transient and continuous dopant dispensing
- To design analytical methods for using PZX dispensing to deliver predetermined IMS concentrations of commonly used dopants
- To control the monomer/dimer ionisation processes of 2-butanol as a candidate dopant in differential mobility spectrometry (DMS)
- To use (R)-(-)-2-butanol as a dopant for chiral resolution of the R and S enantiomers of 2-octanol.
Chapter 2

Theory governing IMS: mobility, sampling, ionisation and dopants

2.1 Introduction to IMS

IMS incorporates a range of gas-phase ion separation and detection (quantitative and qualitative) techniques, normally occurring at ambient pressure [9,19-20]. Samples are introduced to an ionisation region commonly in their gaseous form through a transporting media. An ionisation source in this region provides the energy for generating ions representative of the sample which may be subsequently detected. The identities of the generated ions are dependent upon the type of ionisation source and the chemistry of the supporting atmosphere. These ions are moved by various forces through a drift region, where they are physically separated on the basis of their average drift velocity [9,21]. In addition to the kinetic forces administered by the transporting media (commonly a transport gas), an electrostatic field gradient is applied parallel to the drift region, which supplies the potential for ion mobility. A drift gas is often applied counter-current to the direction of ion travel to ensure that the drift region is kept free of contaminants. Ions collide with the drift gas to retard their movement along the drift tube, with the effect of separating them according to their size, conformation and charge [9,19,22].

Ion swarms exiting the drift region are detected by means of a Faraday detector plate, where the discharged current is proportional to the number of ions over two to three orders of magnitude [9]. IMS spectra are therefore displayed as 2-dimensional plots of signal intensity (in mV or pA) against drift time. Figure 2.1 represents a schematic of the functionality of a linear drift tube ion mobility spectrometer, and Figure 2.2, an example spectrum obtained from the analysis of a set of three ketones in a headspace sample of diesel.
Figure 2.1  Schematic of a typical drift tube ion mobility spectrometer. Taken from Koimtzis [23].

Figure 2.2  Example positive mode linear IMS spectrum taken from the dynamic headspace sampling of three ketones added as fuel markers to a diesel sample, each at 50 ppm(v). The graph shows a typical IMS spectrum of signal intensity vs drift time. RIP denotes the reactant ion peak; A, B and C correspond to responses from 2-butanone, 4-heptanone and 2-decanone. The RIP is $\text{[NH}_3\text{]}^+$ as the IMS cell was doped with ammonia.
Drift times of ion swarms in IMS are in the order of milliseconds, making it a rapid separation and detection technology [24]. Coupled with instrumental operation at ambient pressure, these facets make IMS a suitable technology for in-field analysis. They are also employed as a rapid pre-separation technology for mass spectrometry [25]. Several variations of IMS exist, including travelling wave IMS [26], high-field asymmetric waveform IMS (differential mobility spectrometry) [27] and transverse (or aspiration)IMS [28]. Although the physical conformations of these techniques vary, they all exploit principles of ion mobility, and these are described in detail in Section 2.3.

The principles of IMS may be thought of in four distinct stages: sampling, ionisation, separation (mobility) and detection. Sampling is a fundamental consideration in IMS, as ions are formed, separated and detected in the gaseous phase [9]. It is a requirement that the sample must be delivered in an ionisable form. The supporting environment in the IMS cell must also be maintained through the sampling approach, which requires control of temperature, pressure, humidity and flow rates. A detailed review of sampling processes in IMS is given in Section 2.4.

The identity of ions formed in IMS is dependent upon the ionisation source and energy (eV), the sample and the supporting chemical environment [9] (e.g. humidity). Water molecules present in the supporting atmosphere are ionised to provide a reservoir of primary reactant ions from which sample molecules may acquire charge [12]. The propensity for charge transfer is dependent upon the relative proton (PA) and electron affinities (EA) of the reactant ions and the sample molecules. Sample ions may only acquire charge if their PA or EA, expressed in kJ mol⁻¹, is greater than that of the primary reactant ions [9, 12]. Reproducible charge transfer (APCI) processes are therefore dependent upon the chemical control in the supporting atmosphere. These processes can be optimised for a given analytical application by introducing an alternative chemical species into the supporting atmosphere. This species, termed a ‘dopant’ can provide selective charge transfer, as it raises the PA or EA boundaries in the supporting atmosphere [22, 29]. The dopant species can therefore be used to suppress ionisation from sample matrices and enhance the detection specificity and sensitivity for target analytes. Details of ionisation chemistry and dopants are presented in Section 2.5. The studies in this thesis focus on a novel approach for dopant introduction in IMS systems, through developing the concept of PZX pico-dispensing for IMS. Section 2.6 explores the potential benefits for dopant introduction using PZX dispenser technologies.
chapter provides detailed summaries of applications of dopant chemistries and the techniques used to administer them.

2.2 History of IMS

Following the discovery of x-rays in 1895, [30] Ernest Rutherford was able to measure the mobility of gaseous ions in ambient air through x-ray exposition [31] in 1897. In the same year, JJ Thompson was experimenting on the conduction of electricity by ionising gases. Using two parallel plates separated by a distance of 16 cm, one of which was connected to a supply of 220 V, and the other to an electrometer, he measured the time taken for the ions to reach the electrometer plate under the applied electric field. These experiments formed the first investigations for measuring the mobility of ions in ambient air. The hypothesis was that the change in electrical conductivity properties of atmospheric gases was due to the formation of charged species [32]. These studies were followed by a string of communications describing other ionisation sources such as corona discharge [33] and ultraviolet radiation [34], to measure the mobilities of both positive and negative ion species.

The effects of electrical conduction on the ionic properties of gases developed the understanding that the movement and composition of an ion species is governed by the composition of the gas through which that ion moves [35]. By 1938, this hypothesis had received experimental validation, through papers describing the phenomenon of ion clustering through ion/molecule interactions, [36-37] the effects of humidity on ion mobility [35], and even work on collision theory of the ions with neutral gas molecules [38]. A key theoretical development which governs the validity of IMS today was described by Tyndall [36] in 1938. He investigated the effect of the ratio of the applied electric field to pressure (number density of the gas), $E/N$, on the mobility of eight monoatomic ions, and proved that mobility was independent of $E/N$ (or $E/Td$, where 1 Td = 10^{-17} V cm^2) in low electric field ratios of between 2 and 4 Td (described in Figure 2.3). Despite the initial interest and advancements in ion mobility theory, the advent of mass spectrometry by Thomson in 1933 [39] superseded the pursuit of establishing complex interactions at ambient and elevated pressures.
Figure 2.3 Plots of the ion mobility coefficient, $W_p/E$ (in units of cm$^2$ V$^{-1}$ sec$^{-1}$), against the electric field to number density, $E/Td$, for ions in helium. The data show desolvation of ions with increases in mobility above a threshold of $E/Td$, which is ion specific. Data obtained from Tyndall [36], and expressed in Eiceman and Karpas [9].

Although fundamental relationships between ion mobility and gaseous composition were beginning to be understood, it was not until 1948 that the relationship between ion identity and ionisation chemistry was discovered. In hypothesising a connection between atmospheric breezes and human disease, the physicist Lovelock developed an anemometer device to detect perturbations in air flow. Changes in wind speed caused a displacement of ions between a $^{63}$Ni β-radioactive source and wire collectors in the device, measuring a change in current that was proportional to breeze strength [40]. Lovelock found that the current responded sensitively to halocarbons in the atmosphere, and that the ionisation source was selective to producing negative ions from this class of compound. Although the study provided evidence of a link between the ion source and product ion identity, no drift tubes were used to collect and decipher mobility readings. At this stage, IMS still did not possess drift tubes for characterising generated ion species.
In the 1950s and 1960s mass spectrometry was proving a powerful tool for studying reaction products of ion/molecule interactions at ambient and elevated pressures [41-43]. The developments of drift tubes to enable these molecular associations were mainly designed as an ion path for mass spectrometers rather than drift regions for mobility systems [44]. A number of foundational studies at the time focused on injecting ions through principles of electron bombardment into a drift tube to identify and quantify interaction potentials between mono- and di-atomic ions and neutral drift gases [45-48]. Experimentally determined collisional cross-sections of the ions Ar+, Ne+, N2+ and O2− were achieved by Kaneko et al [49] in 1966. They used a drift tube of 11 electrically-isolated grids through which a linear electric field was applied to determine mobility of these gaseous ions and measure their cross-sections. The design employed two ion gates; one for injecting the ion swarms into the drift tube, and another at the exit to which a RF mass spectrometer was attached. The ion currents at the exit aperture were measured to calculate the cross-section, $\Omega / \Lambda^2$, with prior knowledge of the gas density in the drift region.

The basis for the design of the modern drift tube in IMS is largely attributed to McDaniel et al [50] at the Georgia Institute of Technology in 1958. They used a set of parallel, electrically-isolated rings, to which a homogenous electric field was applied. The first ion mobility spectrometer using a similar drift tube design was described by Cohen and Karasek in 1970 [51]. $^{63}$Ni sources were used to ionise trace molecules in a carrier gas of air containing ppm(v) levels of water vapour. A drift gas of N2 at atmospheric pressure was used and drift spectra with drift times in the order of milliseconds were observed. The detection limits of organic molecules in the order of 1-10 ppb described in these studies emphasised the sensitivity of IMS systems that still underpin one of the attractive aspects of the technique.

The underlying theory of this work was presented in detail by Revercomb and Mason in 1975 [52]. Early descriptions of these instruments coined the term “plasma chromatography” [53-54], due to the separation capabilities of positively and negatively charged species. This term invited unrealistic comparisons with established techniques of higher resolving powers such as GC and time-of-flight MS, and led to a wane in popularity for establishing IMS as an analytical technique in the early 1980s. However, advancements in electrical signal processing capabilities and detection systems, as well as improved drift tube designs to minimise hysteresis effects led to a revival in providing a commercial basis for IMS instrumentation [9]. Although resolving powers could not match gas chromatographic techniques, IMS
devices had the inherent in-field advantages of sub-second analyses and did not necessitate large power requirements in terms of vacuum pumps that were required for mass spectral analysis. With advancements in electrical engineering, the devices were also made more portable through the reduction in size.

Graseby Electronics (later Smiths Detection) was one of the first companies to employ a commercial fieldable ion mobility spectrometer, through the arrival of the chemical agent monitor (CAM) in the early 1980s. The device was used to monitor chemical warfare agents, hydrogen cyanide and mustard gases at atmospheric concentrations of between 0.005 mg m\(^{-3}\) and 11.0 mg m\(^{-3}\). The success of this instrument was due to its detection limits in the order of 100 ppt [55], self-contained fully portable components and the ability to enable rugged use in hostile conditions by untrained personnel. A schematic of the functionality of the CAM is shown in Figure 2.4. The arrival of the CAM paved the way for the development of other portable IMS devices, such as the Vapour Tracer™ produced by General Electric Ion Track [56], and the Smith Sabre 4000 [57]. Varieties of these instrumentation are currently on the market, principally employed for the detection of explosives [58], narcotics [59] and toxic waste substances [60].

Following the events of September 11\(^{th}\) 2001, the perceived need for heightened security measures meant extra demands on the development of more advanced analytical instrumentation. The complimentary, but fundamentally distinctive, technique of differential mobility spectrometry (DMS) had emerged from Russia in the early 1990s [61], and offered the advantages of greater sensitivity and design simplicity than IMS. Ion separation in DMS takes advantage of the dependence of ion mobility, \(K\), on \(E/N\) at high electric field strengths [62]. The differential mobility of an ion swarm under an applied oscillating RF field at low and high field conditions forms the basis for ion separation. A further distinct difference between the two techniques is that a carrier gas flow forms the kinetic energy for the drift of ion swarms towards the detector in DMS, rather than the applied electric field [62]. The fact that both ion mobility techniques exploit different properties of an ion make them complimentary approaches, and as such, both instrumentations are in commercial and academic use throughout the world.
2.3 Underlying theory of ion mobility

2.3.1 Motion of ion swarms under a weak electric field

Ion swarms in IMS traverse the drift tube under the influence of a weak electric field (Figure 2.1). Several forces act on these ions to increase or decrease their velocities. This velocity is the characteristic feature for identification and separation of ions in IMS. A weak field is defined [63-64] where the ratio of the imparted electric field over the number density of the drift gas, $E/N < 2$ Td. Under these conditions, the energy imparted on the ion by the applied field is insignificant compared to the thermal energy possessed by the ion [9]. Its drift velocity, $V_{dr}$, in cm s$^{-1}$, will be proportional to the magnitude of the electric field, $E$, in V cm$^{-1}$ (Equation 2.1).

$$V_{dr} = KE$$  

Equation 2.1
where, $K$, in cm$^2$ V$^{-1}$ s$^{-1}$, is the mobility coefficient of the ion swarm [9]. In addition to forces applied by $E$, ions move through the drift tube under diffusive forces along a concentration gradient, as described by Fick’s first law (Equation 2.2):

$$J = -D \nabla n$$

Equation 2.2

where, $J$ is the number of ions moving down the concentration gradient in units of cm$^2$ s$^{-1}$, $\nabla n$ is the concentration gradient, in mol m$^{-3}$, and $D$ is the diffusion coefficient, in cm$^2$ s$^{-1}$. $K$ and $D$ are related by the Nernst-Townsend relationship, described in Equation 2.3:

$$K = \frac{eD}{kT}$$

Equation 2.3

where, $e$ is the ionic charge, $k$ is the Boltzmann constant, and $T$ is the absolute gas temperature in K [9,65]. Equation 2.3 shows the dependence of ion mobility on the gas temperature inside the drift tube. Ion mobility is directly proportional to the diffusion coefficient. While diffusive and electric field forces move ion swarms along the drift tube, collisions of the ions with neutral gas molecules in the supporting atmosphere cause retardation of the ions, reducing their velocity[66]. Upon collision, the kinetic energy gained by the ion through $E$ is lost to the neutrals, which is then regained successively between collisions. $K$ is inversely proportional to the number density, $N$, in mol cm$^{-3}$, of these neutral molecules. The mobility of an ion swarm drifting through a gaseous atmosphere in a weak electric field with these forces considered is given by the Mason-Schamp equation [67,52]:

$$K = \frac{3e}{16N} \left( \frac{2\pi}{\mu kT} \right)^{1/2} \frac{1}{\Omega}$$

Equation 2.4

where, $\mu$ is the reduced mass of the ion – neutral collision pair, in kg. This is a factor with a marginal effect as it tends to the mass of the neutral drift gas molecule as the molecular weight of the ion cluster increases beyond 300 amu [68]. $\Omega$ is the average collision cross-sectional area, in cm$^2$, of the ion cluster. In experimental work, ion mobility is described in terms of its reduced mobility, $K_0$, due to the dependence of $K$ on $T$ and $N$ [69]. By normalising the reduced mobility to standard temperature (273.16 K) and pressure (101.38 kPa), comparisons in mobility can be made by operating the
spectrometers under different conditions [70-71]. $K_0$, with units of cm$^2$ V$^{-1}$ s$^{-1}$, is defined in Equation 2.5:

$$K_0 = K \frac{273.16}{T} \frac{P}{101.38}$$  \text{Equation 2.5}

where, $P$ is the actual pressure inside the drift tube, in kPa.

2.3.2 Effects of temperature and pressure on mobility

An increase in gas temperature inside the drift tube enhances the kinetic energy of the ions and neutrals [9], leading to a greater number of ion–neutral collisions / cm$^2$ s$^{-1}$. Additionally, temperature also influences the clustering process, causing a change in the identity of the ion swarms [72-73]. The relationship between temperature and clustering has been shown to be a non-linear process [9,72]. This process is complicated by the fact that the addition of a fixed cluster molecule (e.g. (H$_2$O)$_3$) to a small ion will affect the reduced mobility more than that of the same cluster molecule with a heavier ion [72,74]. In other words, while the effect of clustering is non-linearly dependent on temperature, the effect of clustering on the reduced mobility is dependent on the ion mass. Further, an increase in temperature may also dissociate the product ion into clusters of various masses, leading to the detection of fragment ions [72]. The observed behaviours for clustering are also dependent upon the composition (specifically the polarisability) of the drift gas molecules [24].

The basis for determining the effect of pressure on ion mobility is derived from ideal gas laws, provided that the temperature inside the drift tube is kept constant (Equation 2.6).

$$pV = nRT$$, rearranged to give

$$p = \frac{n}{V}RT$$  \text{Equation 2.6}

where, $p$ is the pressure inside the drift tube, in kPa, $n/V$ represents the concentration of neutral drift gas molecules, in mol cm$^{-3}$, and $RT$ is the gas constant at constant.
temperature, in K [75]. Reducing the concentration of gas molecules increases the mean free path length between ion–neutral collisions [76]. The effect is a linear increase in the velocity of the ion swarms, and therefore a linear increase in $K$ with a decrease in pressure [23]. On a practical level, IMS is conducted at close to ambient pressure, meaning that pressure effects are not often a tangible consideration. However, when used as a hyphenated technique with mass spectrometry, drift tube pressures can fall below ambient [9].

2.3.3 Transverse IMS

Linear IMS systems require a highly uniform electric field to enable the accurate drift time calculations. The engineering complexity required to generate these conditions make these devices expensive ($5,000 to $50,000 at the time of writing). A simpler design, known as a transverse or aspirationIMS, has been developed, most notably in Finland during the early 1990s using a printed circuit board approach[77-78]. In the aspiration method, a vapour sample enters the IMS cell through a series of parallel capacitors, each creating a predetermined weak electric field, orthogonal to the sample flow. The electric field is produced by the potential difference between the capacitor units, and is non-uniform. The ions are constantly and simultaneously collected by the capacitors, which are effectively separated on the basis of their mobility [28]. Small ions with higher mobility are deflected to a greater extent than heavier ions, and are therefore collected on the nearest electrodes to the direction of flow, producing a current which is proportional to the number of ions to around two orders of magnitude, see Figure 3.18.

IMS spectra are collected as a measure of current intensity (in pA) at each collector electrode, effectively building a detection “fingerprint” of the sample. Positive and negative ions may be measured simultaneously[79]. Despite being cost-effective instrumentation, there is a limitation of poor resolution, as resolution is limited to the number of collector electrodes in the instrument. Typical instruments only possess 8 electrodes in either the positive or negative modes, and resolution (R) values are ~2-3, compared to R ~10-15 with linear drift tube instruments [79].

Due to their relative small size and cost (around $3000 at the time of writing), transverse IMS devices have principally been used for in-field analyses for measuring VOCs in air [28,78,80]. A recent study used an aspiring IMS to detect a
series of chemical warfare agents, including sarin (2-(Fluoromethylphosphoryl)oxypropane) and lewisite (2-chloroethenyldichloroarsine) in purified dry air (20 ppm relative humidity) at concentrations as low as 15 μg m⁻³. The device used an ion focusing region by means of a 100 μm × 5 mm aperture to condense the ion flow in the carrier gas before the separation region [28]. A drift gas was employed to prevent sample expansion. The condensed ions were focused towards a detector electrode through the drift gas as ion beams under the transverse electric field. This method improved the resolving power of previous aspiration devices without a drift gas (R = 2.4 for the positive reactant ion). Transverse IMS devices have been used for the discrimination of air samples with and without bacterial strains [79], and for on-line monitoring of fermentation processes.

2.3.4 Ion mobility in high electric fields for DMS

The mobility relationships for IMS given by Equation 2.4 only hold for weak electric fields, where \( E/N < 2 \) Td. At higher electric field strengths, the mobility coefficient, \( K' \), becomes dependent on \( E/N \), and classical mobility theory no longer holds. Under high field conditions, the electric field dependence on mobility is non-linear [27,62], and is described by Equation 2.7:

\[
K' \left( \frac{E}{N} \right) = K(0) \left[ 1 + \alpha \left( \frac{E}{N} \right) \right]
\]

Equation 2.7

where, \( K(0) \) is the mobility coefficient, in cm² V⁻¹ s⁻¹, under zero field conditions, and \( \alpha \) is a specific coefficient of even powers of the electric field [27]. This so-called alpha-function is used in DMS to describe the dependence of \( K' \) on \( E/N \) [81].

In DMS, (also termed high-field asymmetric waveform ion mobility spectrometry [82] (FAIMS)) the alpha-function is utilised to separate ions based on their differences in mobility between low and high field conditions. The technique was first described in Russia in 1991, and demonstrated experimentally in 1993 [61]. Early studies demonstrated that at high field strengths, product ions from analytes such as ketones produced higher mobility coefficients than thermalised ions at lower values for \( E/N \). The reasons for higher values for \( K' \) under high fields were related to a decrease in the collisional cross-section, \( \Omega \), of the ion swarms [83-84]. Under these conditions, the effective temperature for the non-thermalised ions increased, causing the fission of

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weakly-bound ion clusters. The removal of water molecules from a hydrated ion cluster decreased the value for $\Omega$, and lead to an increased mobility. This principle is graphically demonstrated in Figure 2.5, which shows a preliminary model for positive alpha-functions, where the ion core is clustered in low field conditions and declustered in high fields. These principles have been supported by empirical evidence with mass spectrometry data which showed that the ion core was unchanged [9,82].

In other experiments, the alpha-functions for a series of ketones with increasing carbon number were modelled to demonstrate the declustering process at high fields (Figure 2.6). It was shown that alpha values of ketones with carbon numbers of 3 and 4 changed more than four times those of carbon numbers 9 and 10 over $a\mathcal{E}/N$ range 0-100 Td [82]. This type of data is to be expected from a declustering process involving $n$ molecules of H$_2$O, as the relative molar fraction of water in a cluster involving smaller ketones will be larger than in a cluster ion in a larger ketone.

\[ \Omega \downarrow \]

\[ E_1 \quad E_2 \]

\[ \Omega \uparrow \]

**Figure 2.5** A graphical model for positive alpha functions. An ion core is declustered at high field ($E_1$) and re-clustered at low field ($E_2$). The ion core is decreased in the low field, leading to a decrease in the cross-sectional area, and increased mobility, $K'$. 
Figure 2.6  Example of field dependence of ketone monomer ions at atmospheric pressure in air from acetone to decanone. The numbers on the graph represent the number of carbon atoms in the molecule. The data shown are representative of the models demonstrated in reference [82].

Experimentally, DMS separates ions by applying an alternating low field / high field waveform in the DMS cell [27]. Ions are formed from the same processes as in IMS, commonly using a $^{63}$Ni source [85]. The low field conditions [62] are around $1000 \text{ V cm}^{-1}$, and the high field, $30 \text{ kV cm}^{-1}$. A carrier gas flow of filtered air or N$_2$, operating at around $300 \text{ cm}^3 \text{ min}^{-1}$ is used to transport the ions through a set a parallel conducting plates, to which the alternating RF waveform is applied [86]. Ions exhibit differential mobility through the clustering / declustering process upon application of the wave. This results in a net migration of an ion swarm towards one of the plates, as demonstrated in Figure 2.7. The ion is neutralised if it collides with either plate, resulting in a loss of signal. To compensate for this drift and allow for detection, a secondary voltage, termed a compensation voltage ($V_c / V$), is applied orthogonally to the RF wave [27, 62]. The compensation field ($E_c / V \text{ cm}^{-1}$) required to enable a stable trajectory of an ion through the DMS cell is indicative of the ion, and is the basis by which ion identification is achieved in DMS [87]. DMS spectra are therefore represented by plots of signal intensity (mV) against $V_c$ (V). If GC is used as a sample introduction technique, a 3-dimensional data surface is generated, with signal intensity on the $y$-axis, $V_c$ on the $x$-axis, and retention time (min) on the $z$-axis. There is no shutter or aperture grid required in DMS cells, meaning that ions are continuously monitored in real time.
2.3.5 Applications for DMS and its advantages for in-field analysis

The selective transmission of ions as a function of the compensation voltage required to permit their detection is a benefit over IMS separations, where all ions generated per unit time are detected simultaneously. This increases the signal/noise (S/N) ratios by simplifying spectral responses. This was experimentally confirmed through the analysis of bromate, chlorate and iodate ions in drinking water disinfectant [88]. Using an RF voltage of 3000 V, all three ions were separated in the negative ionisation mode at Vc values of 20.0, 24.9 and 15.5 V respectively. Details of RF and compensation fields were not described. Detection limits were shown in the order of 3.0 to 71.0 ppb, at S/N of 3-4 times that of EPA analysis. The DMS method virtually eliminated background inferences in the spectra. Ion separation by DMS has been used in hyphenated techniques with mass spectrometry [89-91]. The separation of structural isomers is a particular advantage for IMS and DMS as a pre-separation stage, as isomers possess different spatial conformations and cross-sectional areas. Compensation voltages at a particular RF field can be fixed to provide selective transmission of ions of interest into the mass spectrometer. DMS separations also occur in the order of milliseconds, making them more suitable for specific high-

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throughput analyses than chromatographic techniques with mass spectrometry [10,92].

Micro-fabricated DMS devices are particularly suited as field-deployable devices for the analysis of volatiles due to their size (DMS cells are typically in the order of 2-5 cm in length), compatibility with GC and other sampling inlets, and design simplicity [93-94]. A further advantage of DMS is the possibility of simultaneous detection of positive and negative ions, which can provide additional information about analyte structure and simultaneously detect analytes in the positive and negative mode which are unresolved at a specific compensation voltage. This is not possible in linear IMS instruments.

2.4 Sample introduction for IMS

2.4.1 Considerations

IMS separates ions in the gaseous phase that are formed from molecules delivered to the ionisation region of the spectrometer [9]. It is a requirement that the interface from the inlet source must be capable of delivering an ionisable sample either directly as a vapour or in the vapour phase upon sampling in the drift tube [95-96]. Although most IMS devices function at close to atmospheric pressure, the cells must still be isolated from the ambient environment. The physical environment in the spectrometer (pressure, humidity, temperature) must be kept constant to regulate ion/molecule reaction processes and ion mobilities through the drift tube [9]. The control of humidity is an especially important consideration as the extent of hydration of ions affects their size and hence mobility [97]. Other considerations for choosing suitable sample introduction techniques are the properties of the target analytes (concentration, vapour pressure, thermal stability and proton/electron affinities), the properties of the analyte matrix, and operational efficiency of the device, including power consumption and running costs [9]. Enrichment of the analyte concentration (see Section 2.4.4) is another criterion that may be considered when characterising trace levels of analyte. Various sampling designs have been employed in IMS for sampling of gases, liquids and even solids. The direct sampling of atmospheric gases is only used when monitoring trace impurities in air.
2.4.2 Membrane approaches

Selective sampling using semi-permeable membranes has been proven to maintain the gas purity inside the instrument. In membrane-based approaches, the membrane is permeable to the sample but not the ambient air, meaning that the ion/molecule chemistry is independent of the sampling process. The seminal work for membrane sampling in IMS was described by Spangler and Carrico in 1982 [98]. Their device used 25 μm thick dimethylsiloxane and polypropylene films to sample unfiltered laboratory air to demonstrate the simplification of positive and negative reactant ions with the addition of these membranes. Both membranes excluded chloride [(H₂O)nCl]⁻ and nitrate [(H₂O)nNO₃]⁻ from the background spectrum in the negative mode. More recent studies have focused on introducing membrane inlets for online and in-field monitoring [99]. The control of membrane temperature is an important requirement for regulating humidity in the IMS cell, as the concentration of [(H₂O)n]⁺ is directly proportional to the permeability coefficient [97]. A potential limitation for using membrane approaches is in the analysis of polar target analytes, which have reduced permeabilities within membranes. Poor analyte solubility in the membrane can reduce sensitivity due to reduction of the flux into the ionisation source. Poor yield can be beneficial in specific applications by extending the linear dynamic range (LDR) of the analyte response. A study by Bocoş-Biţanţan et al [100] enabled chloride ion responses within the linear range at beyond 100 mg m⁻³.

2.4.3 Sheath-flow inlets

A “sheath-flow” inlet enables LDR to be controlled over 3 orders of magnitude [101]. A sheath gas of clean air, in a similar configuration to that used as a nebuliser gas in electrospray sources, was added at flow rates of between 10 cm³ min⁻¹ and 60 cm³ min⁻¹ to analyte effluent from a capillary column, transporting the eluting vapours to an IMS cell with a counter current drift gas flow [101]. At high sheath flows, the sample was carried efficiently to the ⁶³Ni ion source, and well mixed with the reactant ions. Decreasing the flow caused the effluent to flow back along an external concentric tube, away from the reactant ions. Normalised chloride product ion intensities were reduced by as much as four times at an average maximum dichloromethane concentration of 3.40 g m⁻³ using a sheath-flow rate of 60 cm³ min⁻¹ without sacrificing the sensitivity of detection. The advantage of this technique lies in the dynamic control of vapour concentrations.
2.4.4 Methods for analyte pre-concentration

The analysis of trace levels of volatile organic compounds (VOCs) in ambient atmospheres usually necessitates a pre-concentration stage to enable their characterisation by current analytical methods. Pre-concentration techniques in IMS use thermal desorption methods to trap VOCs onto an adsorbent surface, the chemistry of which has been preselected to enable an optimal affinity for analyte molecules whilst retaining as little of the matrix as practicable [102-103]. Thermal desorption methods are now standard analytical procedures for GC[104]. The sample is carried via an inert flow of either N\textsubscript{2} or purified air towards the adsorbent, maintained at a cool temperature (normally between -10 °C and 25 °C). The temperature of the adsorbent is then increased to around 300 °C at a rate of 100°C s\textsuperscript{-1} to rapidly desorb the trapped components, which are transported to the analyser under a secondary flow of inert gas. The degree of pre-concentration, \(CF\), is defined by Equation 2.8:

\[
CF = V_f \left( \frac{Y}{V_c} \right)
\]

Equation 2.8

where, \(V_f\) is the sampled volume, \(Y\) is the trapping efficiency for the target analyte and \(V_c\) is the volume of the carrier gas, post-trap [9]. A split flow may be required before and/or after the cold trap to enable better control of the vapour concentration at the ion mobility cell. The considerations for enabling thermal desorption methods in IMS are for complete desorption of all matrix components, such that memory effects are avoided, a low affinity of the adsorbent material for water, to reduce effects on ionisation and ion mobility, and that the material is inert at high desorption temperatures to prevent the formation of artefacts. A proposed example study of using thermal desorption methods to pre-concentrate chemical taggants in fuel samples is described in Section 6.7.

2.4.5 Gas chromatography

GC as a sample introduction method for IMS was first described by Karasek and Keller in 1972 [105]. Today, GC is considered intrinsically compatible with IMS, since the carrier gases do not typically ionise in the ion mobility cell and typical on-column masses in the pg-ng range do not overload the cell and saturate the IMS responses
The pre-separation of analytes in the GC column also simplifies IMS spectra and adds extra dimensionality to the data. The column effluent is introduced directly into the reaction region of the cell using fused silica tubing. Using unidirectional flow of drift gas, the volume of the reaction region is rapidly purged of excess, lowering the residence time of sample in the reaction region by virtue of the velocity of the gas flow [106-107]. This reduces peak broadening, decreases the opportunity for ion/molecule clustering in the drift cell, and provides a repeatable residence time of sample in the reaction region. A schematic showing coupling of a GC column to an ion mobility cell using unidirectional flow of drift gas is presented in Figure 2.8. Another feature which emphasizes the compatibility of GC with IMS is that there is a negligible pressure differential between the two devices; pumps are normally not required, and interfacing is achieved more simplistically. For these reasons, GC interfaces to both IMS and DMS systems are currently commonplace in commercial instruments [108-109].

![Figure 2.8 Laminar design for connecting capillary GC to a time-of-flight ion mobility spectrometer. Adapted from Eiceman and Karpas [9].](image)

### 2.4.6 Sampling techniques for liquids

Interfaces have been developed for IMS which dispense liquids either directly into the ionisation source, or contain an intermediate stage which efficiently volatilises the sample. Direct liquid injection can rapidly overload the ionisation source as at ambient pressure, liquids have higher densities than gases of >three orders of magnitude [9]. It is therefore a requirement that liquids must be introduced at volumes typically below 1 nL, and that efficient volatilisation and ionisation in the gaseous state be produced with negligible formation of aerosols. Electrospray...
ionisation (ESI) is simultaneously a liquid sample injection and a unipolar ionisation technique that has proved successful in IMS for the analysis of peptides and other bioorganic molecules [110-112]. ESI uses a liquid flow of around 50 μL min⁻¹ which is nebulised through a capillary tube at high potential. Droplets formed at the electrospray source meet a desolvation gas flow of N₂ at temperatures of between 150 °C and 400 °C to form product ions that can be characterised for mobility in the drift region. The technique is most suitable for non-volatile components such as bio-polymers, but produces practical challenges in optimising the electrospray parameters to enable maximum desolvation and yield of product ions. The parameters that require optimisation are the bias voltages, sample flow rate, desolvation flow rate and temperature [55].

A recent sampling development for IMS [113] has used PZX dispensers to calibrate responses of explosive standards of cyclotrimethylenetrinitramine (RDX), pentaerythritol tetranitrate (PETN) and trinitrotoluene (TNT). The study used an array of six PZX nozzles containing the explosives in solutions of isobutanol at concentrations of 10.0 mg dm⁻³. Droplets of 97 pL were dispensed on-demand at a ceramic-coated surface, heated to 250 °C to rapidly vaporise the samples, and make them suitable for ionisation in an IMS cell. The waveform frequencies of the dispensers operated between 50 Hz and 3000 Hz, generating known vapour concentrations of 1.2 – 18.9 ng dm⁻³. The study firstly involved optimising the reproducibility of the droplet volume by conducting a 3-factor central composite design approach of eight levels, where the pulse amplitude, pulse width and dispensing (waveform) frequency formed the factorial inputs to the model. No definition was given for droplet volume reproducibility, but the droplet volumes were visually defined by using a calibrated charge couple device camera with 200× magnification. Pulse width was determined to affect droplet volume considerably, with a difference of 110 pL over the range of 30 – 50 μs.

Once vaporised, the dispensed material was transported to the IMS at 10 dm³ min⁻¹. Whilst explosive vapour calibration was enabled by the novel sampling technique, with linear IMS responses (in a.u.) for the product ions of R² = 0.6 – 0.99, the design of the device suffered several limitations [113]. Sampling times of up to 60 seconds were required to enable calibration responses, producing relative errors in signal reproducibility of around 10% RSD. The device temperature of 250 °C was also shown to decompose the structure of PETN into nitrate ions, complicating sample analysis. A further drawback was elaborate instrumental design which included
numerous component parts and high expense. The principle advantages for this technique were the on-demand generation of vapour standards over more than six orders of magnitude, demonstrating flexibility of the approach with minimal sample preparation [113].

2.5 Ionisation theory in IMS

2.5.1 Overview

Atmospheric pressure chemical ionisation (APCI) processes in IMS are dependent upon the ionisation source and the ionisable sample [9]. In instances of doping the spectrometer with reagent gas, the supportive atmosphere of the carrier and/or drift gas may also contribute to the APCI process. The identity of the reactant ions is therefore dependent upon the type of ion source, and many exist in IMS instruments. These include the α and β-emitters, $^{241}$Am [114] and $^{63}$Ni [115], respectively, UV photo-ionisation [116], pulsed corona discharge [117], continuous corona discharge [118], distributed plasma ionisation [119] and electrospray ionisation [Section 2.4.6]. In addition to the source, product and reactant ion concentration and identity is governed by thermodynamic processes. Temperature, pressure and degree of humidity inside the drift tube therefore all affect ion production [72,120]. Despite these complications, models of ion/molecule reactions exist, supported by mass spectrometric data. Reaction processes in $^{63}$Ni are the most studied and understood.

2.5.2 Formation of reactant and product ions in the positive mode

The mean energy distribution of electrons from a $^{63}$Ni source with an activity of 10 mCi is 17 keV [9]. In a standard drift tube containing $\text{N}_2$ as a drift gas, the collision of a $\text{N}_2$ molecule with a single primary electron results in a positive nitrogen ion and a secondary electron with lesser energy (~1 keV), as per Equation 2.9. As only 35 eV are required to produce one thermalised ion pair of $\text{N}_2$, a cascade of nitrogen ions are generated from the subsequent collisions of both primary and secondary electrons with the gaseous atmosphere [121]. The nitrogen ions and thermalised electrons form a reservoir of charge from which all subsequent ionisation chemistry in IMS is derived. The presence of water vapour in the supporting atmosphere results in
thermalised collisions with the generated $N_2^+$ ions, leading to a sequence of reactions as described by Equations 2.10 through 2.14 [9]:

\[
\begin{align*}
N_2 + e^{-}^{(\text{primary})} & \rightarrow N_2^+ + e^{-}^{(\text{primary})} + e^{-}^{(\text{secondary})} \\
N_2^+ + 2N_2 & \rightarrow N_4^+ + N_2 \\
N_4^+ + H_2O & \rightarrow 2N_2 + H_2O^+ \\
H_2O^+ + H_2O & \rightarrow H_3O^+ + OH \\
H_3O^+ + H_2O + N_2 & \rightarrow H^+(H_2O)_2 + N_2 \\
H^+(H_2O)_2 + H_2O + N_2 & \rightarrow H^+(H_2O)_3 + N_2
\end{align*}
\]

Equation 2.9

The extent and rate of formation of the ionic species in Equations 2.11 through 2.14 is governed by the concentration of water vapour in the supporting atmosphere [9,122]. In clean air or nitrogen, the hydrated protons (Equations 2.13 and 2.14) are the dominant reactant ions, and can undergo collisions with analyte substances in the reaction region of the mobility spectrometer. If a compound, $M$, with a proton affinity greater than water (697 kJ mol$^{-1}$) attachment is introduced into this region, containing sufficiently high reactant ion concentration, then a water-based displacement reaction as per Equation 2.15 can occur [9,122]:

\[
H^+(H_2O)_n + M \rightleftharpoons MH^+(H_2O)_n + Z \rightleftharpoons MH^+(H_2O)_{n-1} + H_2O + Z
\]

Equation 2.15

Where, $MH^+(H_2O)_n$ is an electrically excited intermediate adduct ion, which may be stabilised by a third body, $Z$, (normally a neutral gas molecule) to form stable product ions capable of traversing the drift tube [123].

The rate of product ion formation is established by the concentration of hydrated protons and analyte, and by the collision frequency of the reactants in the reaction region. This is the dominant reaction pathway to the formation of positive-polarity product ions in IMS [9]. If the concentration of compound $M$ is increased, the reactant ion reservoir will be depleted due to increased charge-transfer towards the $M$ adduct. This will be consistent with a reduction in the intensity of the reactant ion peak (RIP)
in the mobility spectrum, as well as an increase in intensity for the product monomer. If the concentration of M is raised further, then the monomer can cluster with another analyte molecule, forming a proton-bound dimer cluster complex, as shown in Equation 2.16 [9,124]:

\[
\text{MH}^+(\text{H}_2\text{O})_n + \text{M} \rightleftharpoons \text{M}_2\text{H}^+(\text{H}_2\text{O})_{n-1} + \text{H}_2\text{O}
\]

Equation 2.16

The presence of dimer ions further reduces the RIP and monomer peak intensities, and leads to the characterisation of a dimer peak in the drift time spectrum [123]. A representation of product and reactant ion responses from an analyte vapour, M, generating monomer and dimer ions is shown in Figure 2.9.

![Figure 2.9](image)

Figure 2.9 An idealised plot of the response intensities against sample vapour concentration for producing monomer and dimer product ions within the linear dynamic range (LDR) of the IMS detector response. Region A represents responses within the LDR, and B, where the rate of removal of the reactant ions exceeds their rate of formation. The RIP is represented in red, the product monomer in green and the product dimer in blue.
Once the concentration of reactant ion rises above a critical level (normally in region of 500 ppb to 5 ppm), the rate of removal of the reactant ions exceeds the rate of formation, leading to a depletion in the charge reservoir [9,124]. At this stage, product ion responses are no longer linear with concentration. The result of this behaviour is a limited linear detection range to within 30% to 40% of the total response range in the system, which is, in absolute terms commonly around two orders of magnitude. Beyond this range, logarithmic relationships are used [9]. Figure 2.9 demonstrates this principle with relation to reactant and product ions.

The parameter which determines the formation of protonated product ions is proton affinity (PA)[125-126]. For a neutral gaseous analyte molecule entering the reaction region, PA is defined as the energy released from the reaction in Equation 2.17, and is a measure of the basicity of the compound [9]. The higher the PA, the stronger the base and weaker the conjugate acid in the gaseous phase.

\[ M + H^+ \rightarrow MH^+ \]  \hspace{1cm} \text{Equation 2.17}

Analytes with relatively high PA values have a higher propensity to undergo proton transfer, Equation 2.15. Basic compounds with a PA of greater than 800 kJ mol\(^{-1}\) (e.g. amines, organophosphorous compounds (OPC) and ammonia), yield protonated product ions under kinetic control defined by the collision-rate constant; in the order of \(10^{-9}\) cm\(^3\) s\(^{-1}\) and such compounds ionise quantitatively in the presence of hydrated protons [12]. Kinetic control shifts to thermodynamic control as the PAs of the analytes falls below 800 kJ mol\(^{-1}\)(Figure 2.10). Compounds in this group include water, alkanes and alcohols. Ionisation efficiency, defined as the ratio of free electrons to product ions, of these analytes is lesser than the kinetically-controlled group, and the stabilities of the product ions are weaker [12]. Lower stability means increasing likelihood of ion fragmentation within the drift tube.
The extent of product ion hydration also affects the efficiency of proton transfer [98]. The degree of hydration is dependent upon the PA of the analyte, such that the number of water molecules in the ionic cluster is lower for increasing analyte PA [98]. Another feature of hydration is that proton transfer reactions occur more readily when the degree of hydrative clustering is smaller [9,12]. Both phenomena have been studied in detail using mass spectrometry (IMS-MS) as a secondary detector when analysing the stability of product ions in IMS [9,127] and DMS [128]. It is important to note that the size of cluster ions also depends on the concentration of water in the drift and/or transport gases. The sensitivity of analyte detection is often lower for wet gases due to higher degrees of hydration [9,12].

### 2.5.3 Formation of reactant and product ions in the negative mode

The formation of negative ions occurs through various ionisation mechanisms determined by the electronegativity of the analytes and the energies of the primary and secondary electrons involved, Equation 2.9 [9,129]. In N₂, thermalised electrons carry the negative charge as free species, which ionise compounds leading to compound-specific anions. When air is used as the supporting atmosphere, oxygen...
molecules (electronegativity of 3.44 on the Pauling scale) acquire thermalised free electrons which subsequently hydrate as per Equations 2.18 and 2.19 [9]:

\[
M + O_2 + e \rightarrow O_2 + M \quad \text{Equation 2.18}
\]

\[
M + n H_2O + O_2 \rightleftharpoons O_2(H_2O)_n + M \quad \text{Equation 2.19}
\]

where \( M \) is a neutral gaseous molecule, \( O_2 \) or \( H_2O \). The hydrated ions shown in Equation 2.19 may undergo collisions with other neutral molecules with appropriately high electron affinities [12], to create more stable product anions that result from charge transfer of a molecule with a higher EA than the hydrated oxygen cluster (Equation 2.20). Other common reaction pathways for the generation of negative-polarity IMS responses are the formation of oxygen adducts [130] (Equation 2.21), and the abstraction of protons from the existing hydrated cluster (Equation 2.22):

\[
O_2(H_2O)_n + M \rightleftharpoons M + n H_2O + O_2 \quad \text{Electron transfer} \quad \text{Equation 2.20}
\]

\[
O_2(H_2O)_n + M \rightleftharpoons MO_2 + n H_2O \quad \text{O}_2^\text{−} \text{ adduct formation} \quad \text{Equation 2.21}
\]

\[
O_2(H_2O)_n + M \rightleftharpoons (A-H) + \text{ neutrals} \quad \text{Proton abstraction} \quad \text{Equation 2.22}
\]

The subsequent formation of product anion clusters with water and carbon dioxide may also be seen in the IMS spectrum. The degree of clustering is dependent upon the concentration of \( H_2O / CO_2 \) in the drift tube [65], as well as the relative electron affinities and concentration of the analyte molecules. When highly electronegative species are present in the supporting atmosphere, favoured electron attachment may lead to the reduction in intensity of the oxygen-bound negative reactant ion peak [54]. A form of a dissociative ionisation reaction, halogen presence in the drift tube commonly leads to this phenomenon, shown in Equation 2.23 [22,131]:

\[
\text{Halogen} + O_2(H_2O)_n \rightarrow O_2 + Cl^−(H_2O)_n + \text{fragments} \quad \text{Equation 2.23}
\]
2.5.4 The analytical need for dopants in IMS

Well-established proton and electron affinity scales that were developed for free ions in the gas phase under vacuum conditions have limited value at ambient pressure, as they do not take account of the supporting atmosphere and the phenomena of clustering inside the drift tube [9]. This is a hindrance for producing predictive models for ion formation in IMS and DMS, as PA and EA values alone do not provide complete descriptions. The presence of impurities and the degree of humidity inside the drift tube further complicate the ionisation process and degree of clustering [9,132]. Moisture in the drift gas is also known to degrade the selectivity of ionisation in IMS [9]. These complexities, along with the many potential reaction pathways for ions, described in Equations 2.9 to 2.23, can lead to complicated drift time spectra with reduced detection sensitivity, a lack of specificity for the detection of target ions and the overlap of peaks in samples where multiple reactant and product ion signals are formed [9]. In complex samples, such as hydrocarbon fuels, the presence of hundreds of VOCs leads to multiple ion mobility responses in both positive and negative ionisation modes [133]. The compounds are often not resolvable, even through the introduction of GC as a pre-separation stage [134]. There is therefore a need in IMS, especially in the analysis of complex samples, to impart increased ionisation specificity into the analysis, and this is achieved by altering the chemistry of the reactant ion with the introduction of a dopant vapour into the drift or carrier gas [135].

Dopants alter the relative PA and/or EA of the reactant ions, enabling charge-transfer reactions (Equation 2.15) only to molecules that possess higher PAs and/or EAs than the dopant ions. Alternatively, drift gas composition can be modified to alter the mean free path length of the reactant ions between collisions, changing the mobility coefficient as per Equation 2.4, without altering the chemistry of the ions. Compounds of this type are termed “drift gas modifiers” [136].

2.5.5 Mechanisms for dopant interactions in IMS

When a reagent gas, R, is introduced into the reaction region, the hydrated protons in positive polarity, as governed by Equations 2.13 and 2.14, are converted by
hydration displacement reactions into alternate reactant ions [9,12], as per Equation 2.24:

\[
H^+(H_2O)_n + R \rightarrow R_{m-1}H^+(H_2O)_{n-1} + H_2O
\]

Equation 2.24

where, \( m \) is the number of reagent neutrals in the ion cluster. For Equation 2.24 to proceed, reagent, \( R \), must have a substantially higher PA \((\text{in} \ \text{kJ mol}^{-1})\) than the hydrated proton. If alternative reactant ions are formed, only compounds with greater PAs than these reactants will be ionised through proton transfer [137-138]. This is represented in Equation 2.25. If the enthalpy of association of the compound is much lower than that of reagent \( R \), then the reaction as per Equation 2.24 will not proceed [9].

\[
R_{m}H^+(H_2O)_{n} + M \rightarrow R_{m-1}M(H_2O)_{n} + R
\]

Equation 2.25

where, \( M \) is the analyte molecule. Compounds regarded as matrix interferences in IMS may be eliminated by utilising this principle. Chemical dopants can be introduced into the reaction region that have substantially larger enthalpies of association than the interfering compound, but lower than that of the target analytes. The matrix effects are not seen in the mobility spectrum as they do not participate in the ionisation processes, while the reaction in Equation 2.24 will proceed for the target analyte. The elimination of interferences simplifies the mobility spectra, allowing for improvement in detection selectivity (Figure 2.11) [139-140]. To achieve efficient ionisation of a target analyte while suppressing matrix interferences, careful selection of an appropriate dopant of specific PA is required.
Figure 2.11 Processes of charge transfer during ionisation in positive mode. Adapted from Puton et al[12].

2.5.6 Positive polarity dopants in IMS

2.5.6.1 Acetone

Acetone is ionised by proton transfer, as per Equation 2.15, from water-based reactant ions in IMS; its ionisation exerting an enthalpy of association of 832.6 kJ mol\(^{-1}\) [141]. A summary of the uses of acetone as an IMS dopant is given in Table 2.1.
Table 2.1 A summary of IMS studies utilising acetone dopant chemistry

<table>
<thead>
<tr>
<th>Detected analytes</th>
<th>Analytical benefit</th>
<th>Introduction method and concentration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 organophosphorous compounds (OPCs) in presence of volatile organic interferences.</td>
<td>Increased selectivity due to partial removal of interferences.</td>
<td>Permeation tubes with valves for enabling concentration control, using advanced vapour monitor (AVM). Concentration: 100 – 2000 ppb.</td>
<td>135</td>
</tr>
<tr>
<td>Dimethoate at 40% in VOC formulation.</td>
<td>Enhanced selectivity for dimethoate, and increased resolution from RIP.</td>
<td>Added to carrier gas from permeation sources. Mixtures of acetone-ammonium used at concentrations from 0.3 – 3.0 μg dm$^{-3}$.</td>
<td>138,142</td>
</tr>
<tr>
<td>OPC pesticides.</td>
<td>Enhanced selectivity for analytes due to (H$_2$O)$_n$H$^+$ reduction.</td>
<td>Used as a solvent for the analytes, prepared from test solutions with acetone. Solution concentrations from 0.5 – 500 ppm.</td>
<td>143</td>
</tr>
<tr>
<td>Dimethyl methylphosphonate (DMMP) nerve agent.</td>
<td>RIP and mixed dimer peaks shifted to longer drift times, increasing resolution.</td>
<td>Acetone in drift gas used in the chemical agent monitor (CAM). Acetone delivered using permeation sources.</td>
<td>144</td>
</tr>
<tr>
<td>VOCs in atmosphere.</td>
<td>Showed that elevated PA with acetone and dimethylsulfoxide (DMSO) can completely remove alcohol and VOC interferences.</td>
<td>Mixtures of acetone, ammonium and DMMP reagent gases using permeation sources. Concentrations from 100 ppb to 2000 ppb controlled by needle valves.</td>
<td>145</td>
</tr>
</tbody>
</table>

Acetone was used as a reagent gas to remove atmospheric interferences in the monitoring of chemical weapons agents (CWA). At less than 1ppm in the drift stream, both monomers and dimers of acetone were detected as alternative RIPv [144]. The relatively high PA of acetone in relation to hydrocarbons, esters and alcohols (540-780 kJ mol$^{-1}$) prevented these interfering compounds from participating in proton transfer, simplifying the drift time spectrum, and increasing ionisation selectivity of the analyte. CWA produce ions from acetone reactant ions and reduce the acetone RIPv intensities. A diagrammatic representation of this work, undertaken by Eiceman and Stone [144], is represented in Figure 2.12.
Figure 2.12  Ion mobility spectrum of dimethyl methylphosphonate (DMMP) using acetone as the reagent gas. Acetone chemistry shifts the monomer and dimer DMMP complexes to longer drift times, separating the product ion peaks from the RIP, simplifying the mobility spectrum. Adapted from Eiceman and Stone [144].

The OPC nerve agent, dimethyl methylphosphonate (DMMP), complexed with an acetone dimer at the ppb range to induce a mixed proton-bound dimer, via a displacement reaction as per Equation 2.26. Higher concentrations of DMMP (~1ppm) in the dynamic system led to analyte dimer formation, such as that represented in Equation 2.16. The newly-formed product dimer had a greater mass than the analyte monomer, with a higher cross-sectional area, and lower mobility. This seminal study demonstrated the benefits of acetone as both a dopant and a drift gas modifier [144].

\[
(CH_3COCH_3)_2H^+ + A \rightarrow (CH_3COCH_3)AH^+ + CH_3COCH_3 \quad \text{Equation 2.26}
\]

The RIP and mixed dimer peaks were shifted to greater drift times upon drift gas modification (Figure 2.12). The effect of peak shifting could be used as an advantage with the utilisation of dopants, as overlapping peaks present in clean drift gas spectra were fully resolved with addition of ppm levels of modifier [144]. Changing acetone concentration also impacted upon the levels of hydration, as acetone monomers had
a higher affinity for water than their dimer ions. The degree of hydrative clustering also altered the cross-sectional area, and therefore the resolution of the ion peaks.

The full evaluation of doping efficiency can be seen in complex samples, where multiple chemical interferences are present. In work presented by Eiceman et al [135], a mixture of 19 OPCs were intentionally spiked with a range of PA volatile organic compounds (VOCs). The objective was to examine the relationship between the ionisation selectivity of a dopant gas and its PA when analysing these complex mixtures. The elevation of gaseous PAs with the doping of acetone and dimethyl sulphoxide (DMSO) (885 kJ mol⁻¹), reduced the number of characterised components from 48 to 26 and 20 with the respective reagent, thus improving detection selectivity. Only the VOCs with relatively high PAs (esters and amines) were characterised, and around 35 interference peaks eliminated. In addition, the increase in DMSO concentration from 100 ppb to >2 ppm imparted extra response selectivity [9,135]. DMSO dimers and trimers formed as alternative reactant ions at higher concentrations, altering the degree of hydrative clustering and increasing the analytical space for the resolution of product ions. It was also demonstrated that the relationship between the mass of an ionised compound and the spectrometric signal intensity produced no significant statistical difference when using a dopant (Figure 2.13). The absolute detection limits were between 20-50pg, regardless of the ionisation chemistry used [135]. This is an important outcome, considering that the relatively low detection limits in comparison to other spectrometric techniques are an attraction for IMS.
The simultaneous use of acetone with other dopants has been studied for the detection optimisation of the organophosphorous pesticide, dimethoate [138,142]. This compound was used in a formulation at 40%, and exhibited unresolved product ions in clean air. Under the dopant influence of single reagents, the dimethoate response was <20 × S/N, owing to its relatively low volatility (0.001 Pa at 25 °C), and the presence of a dimethyl benzene impurity which overlapped the dimethoate peak in the drift time spectrum. When acetone was used in combination with ammonia, both at concentrations in the drift stream of 1 ng cm³, responses were seen for only the dimethoate monomer and dimer [138]. All other interferences were eliminated in the spectrum, increasing analyte selectivity, as well as enhanced drift time resolution between the monomer and dimer. Quantitative aspects of detection were also characterised in this research, by mapping the intensity of dimethoate peaks against varying dopant mix concentrations (Figure 2.14). At concentrations of acetone-ammonium dopant of 0.2 - 0.8 ng cm³, the reagents did not occupy the full ion source region, and therefore the analyte was able to participate in proton transfer from hydrated protons, despite their possessing a lesser PA than the dopants [138,142]. The effect of this was a reduction in response intensity. The optimal response observed at a concentration of 1 ng cm³ was succeeded by excess concentrations of
dopant in the ion source, decreasing the analyte signal intensity. This owed to a
dilution effect and complicated ion-molecule interactions between the reagents and
the analytes.

Figure 2.14 Relationship curve between the concentration of ammonium-acetone
dopants and the response of dimethoate. Adapted from Long et al [138].

2.5.6.2 Ammonia
Ammonium ions naturally occur in drift time spectra as low-level (<0.03%) contaminants when using clean air or nitrogen as the drift or carrier gas in IMS [54].
The relatively high PA (853.6 kJ mol⁻¹) of ammonia enables a high efficiency of proton transfer from hydronium ions as per Equation 2.27 [140]. The mobility of these ions at 100°C is around 20% greater than the mobility of hydronium [12]. These physical properties make ammonia a potentially useful candidate dopant for IMS, and various applications are found in the literature. A summary of IMS studies using ammonia as a dopant is presented in Table 2.2.

\[
\text{(H}_2\text{O)}_n\text{H}^+ + \text{NH}_3 \rightarrow \text{(H}_2\text{O)}_n\text{NH}_4^+ + n\text{H}_2\text{O}
\]  
Equation 2.27

Table 2.2 A summary of IMS studies using ammonia dopant chemistry
<table>
<thead>
<tr>
<th>Detected analytes</th>
<th>Analytical benefit</th>
<th>Introduction method and concentration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine and noscapine.</td>
<td>Spectral simplification by enhancing analyte selectivity.</td>
<td>Permeation tube containing ammonium carbamate with diffusion barrier for controlling concentration. Actual concentrations not given.</td>
<td>147</td>
</tr>
<tr>
<td>Pyridine in aliphatic solvents and benzene.</td>
<td>Addition of ammonia reduced number of reactant ions, enhancing sensitivity of product ions of high mobility.</td>
<td>Introduced into the carrier gas stream by passing N₂ carrier gas over a headspace of ammonium hydroxide solution in a flask. Single concentration producing a [NH₄⁺][H₂O][N₂] of 1:847:3 × 10⁴ mol.</td>
<td>148</td>
</tr>
<tr>
<td>Cocaine in the presence of polyaromatics and other amines.</td>
<td>Enhanced resolution of weak product ion.</td>
<td>Introduced by permeation source into the N₂ carrier gas at 3 ppm, and not varied. The study also used naphthalene as a reagent gas at 4 ppm, employing the same method.</td>
<td>149</td>
</tr>
<tr>
<td>Formaldehyde.</td>
<td>Enhanced product ion resolution, due to increased mobility for ammonia RIP.</td>
<td>0.5 mg dm⁻³ ammonia added to the carrier gas stream using permeation sources of ammonium carbamate.</td>
<td>150</td>
</tr>
<tr>
<td>2,3-dimethyl-2,3-dinitrobutane.</td>
<td>Enhanced selectivity for ammonia chemistry. Less dissociation product ions.</td>
<td>Ammonia added to the drift gas at a concentration of 0.61 mg m⁻³, using permeation sources, controlled via needle valves. The study also used the same approach for doping with methylene chloride at 77.3 mg m⁻³.</td>
<td>139,151</td>
</tr>
</tbody>
</table>

The greater mobility of ammonia as a reactant ion increases the analytical space and therefore the potential resolution of product ions. This was observed in studies involving the detection of formaldehyde [150]. In clean air, corresponding formaldehyde signals overlapped the intense hydrated RIP. When doped with ammonium at 0.5 mg m⁻³, the decrease in drift time for the RIP enabled complete resolution of the formaldehyde responses. Dimer reactant ions were formed from increasing dopant ammonia concentrations as described by Equation 2.16. The unique feature of a drift time spectrum involving ammonium dimerisation is that the drift times for the dimer complex are quicker than the monomer entities, due to a higher efficacy for hydrative clustering around the monomer [150]. This phenomenon increases the suitability for ammonia use as a dopant, as the dimer presence does not reduce the analytical space through the drift tube, and may also favour ionisation reactions with analyte molecules, due to lesser degrees of clustering with water.

A common use of ammonia as a dopant in IMS is for the detection of CWA [12]. These applications take advantage of the relatively high PA of ammonia to reduce
ionisation interferences from atmospheric contaminants. Identified interferences in this field include fuel vapours and combustion products with PAs in the order of 500–800 kJ mol⁻¹. Reduced ionisation of these contaminant compounds precludes the risk of false positives, and simplifies the drift time spectra [139,151]. Spectral simplifications through ionisation specificity using ammonia have also been achieved in narcotics detection. A diffusion barrier linking a capsule formulation of ammonium carbamate for controlled release of ammonia was prepared for the characterisation of morphine and noscapine [147]. The method offered limits of detection as low as 0.1 ng, and also demonstrated applicability for simultaneous quantitative analysis, although hypothesised results were not confirmed by IMS-MS experiments. The IMS characterisation of noscapine also resulted in fragmentation of the product ion, due to potential breaking of σ-bonds within the noscapine structure. A comparative study without the use of ammonia in the ion source was not attempted to elucidate whether the fragmentation was related to the ammonia chemistry, or whether product ion stability was increased with the addition of dopant [147].

Various studies have highlighted the value of drift gas modifiers in the stabilising of product ions by increasing their resonance time in the drift tube [100,149,152]. This was seen in the characterisation of molecular ions produced from the dinitroalkane, 2,3-dimethyl-2,3-dinitrobutane [139]. Under water chemistry, the product ions dissociated, and reactant ion mobilities for the hydrated protons broadened, indicating cluster instabilities in the drift region. The dissociation products were not observed to the same extent when the drift gas was doped with ammonia. The work also highlighted the extra degree of ionisation selectivity and peak resolution when using ammonia as a dopant.

2.5.6.3 Other dopants in positive polarity

The relatively high PA (>850 kJ mol⁻¹) of strong bases (e.g. amines) makes them suitable for selective and sensitive proton ionisation in IMS. Their efficacy for proton transfer is such that chemical modifiers with greater PAs than acetone can be used as the dopant, further reducing background interferences and facilitating the sensitivity of the analyte response [12]. A summary of applications using high PA dopants is given in Table 2.3.

<table>
<thead>
<tr>
<th>Table 2.3 A summary of IMS studies using other dopants in the positive polarity mode</th>
<th></th>
<th></th>
</tr>
</thead>
</table>

59
<table>
<thead>
<tr>
<th>Detected analytes</th>
<th>Dopant</th>
<th>Analytical benefit</th>
<th>Introduction method and concentration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biogenic amines of putrescine, cadaverine and spermidine.</td>
<td>n-nonylamine.</td>
<td>Fully resolved spectra. Interferences from vaginal flora removed.</td>
<td>n-nonylamine vapours released from a reservoir tube into the carrier gas stream containing the sample. Concentrations not given.</td>
<td>153</td>
</tr>
<tr>
<td>4 alkanoamine vapours.</td>
<td>4-heptanone.</td>
<td>4-heptanone removed interferences caused by diesel vapours, providing full spectral resolution.</td>
<td>Used a diffusion source of Teflon tubing with 250 μL of dopant adsorbed onto a Porapak Q bed. Effusion rate was measured, giving IMS concentration of 1.3 ± 0.2 ppm.</td>
<td>154</td>
</tr>
<tr>
<td>Trimethylamine, putrescine and cadaverine.</td>
<td>n-nonylamine.</td>
<td>Fully resolved spectra.</td>
<td>Dopant vapours released from reservoir tube, as in reference 154.</td>
<td>155</td>
</tr>
<tr>
<td>Methamphetamine.</td>
<td>Nicotinamide.</td>
<td>Fully resolved and clearer spectra due to high efficacy of proton transfer. Unstable products in water chemistry.</td>
<td>Nicotinamide added in solution as a reactant, and used to calibrate IMS responses. No details on dopant concentration given.</td>
<td>156</td>
</tr>
<tr>
<td>Ammonia in ethylene matrix.</td>
<td>5-nonanone.</td>
<td>Dopant suppresses ethylene ionisation to give more sensitive NH₃ product ion.</td>
<td>Dopant added to drift gas from an open 2 cm³ volumetric flask containing 50 μL of liquid.</td>
<td>157</td>
</tr>
<tr>
<td>Hydrazine (HZ) and monomethylhydrazine (MMZ).</td>
<td>5-nonanone.</td>
<td>Increased resolution due to larger 5-Non-HZ(MMZ) clusters increasing drift time.</td>
<td>Used a diffusion source for the dopant, constructed from PTFE tubing. Concentration range: 0 – 1 ppm.</td>
<td>158</td>
</tr>
<tr>
<td>Amino acids and naturally-occurring sugars of: methionine, atenolol, tryptophan, methyl-α-glucopyranoside.</td>
<td>2-butanol.</td>
<td>Chiral separation of amino acids by using enantiomerically pure 2-butanol as a drift gas modifier.</td>
<td>Infused into N₂ drift gas using a syringe pump. Concentration range: 0 – 14.3 ppm.</td>
<td>29</td>
</tr>
</tbody>
</table>

n-nonylamine (PA = 920.4 kJ mol⁻¹) was used as a modifier for the diagnosis of bacterial vaginosis in humans [153]. Introduced at the ppm range to N₂ carrier gas, n-
nonylamine (Non) provided the proton reservoir for the semi-volatile analyte amines, cadaverine, putrescine and spermidine; biological indicators for the condition. Reduction in the reactant ion peak intensity for NonH⁺, by increase of the amine product ions provided confirmation of the condition with 95.1% diagnostic accuracy (Figure 2.15). The ion mobility of NonH⁺ of 10.9 ms was considerably lower than for the amines (6.6 ms - 8.2 ms) and thus provided fully resolved spectra, whilst eliminating interferences. The same study was applied later in the determination of meat freshness [155]. Amine derivatives have also been applied as drift gas modifiers to reduce product ion fragmentation. This was highlighted in narcotics and chemical warfare agent detection studies [156], where product ions were unstable in water chemistry.

![Figure 2.15 A comparison of ion mobility spectra of a positive and negative test for bacterial vaginosis. Adapted from Zarpas et al [153].](image)

Ammonium reactant ion peaks, corresponding to gaseous impurities, present as the positive ions of quickest mobility when N₂ or air is used as the carrier gas [12]. IMS studies estimating the concentration of atmospheric ammonia at between ~10 ppb and ~1.5 ppm have been achieved, but suffer from the risk of disturbances from hydrocarbon species present in air [156]. These can influence the intensity of the ammonia signals and increase random and systematic errors in quantification. The addition of OPC dopants can aid the accurate quantification of ammonia by suppressing hydrocarbon signals, such as ethylene, where π-systems may interact with reactant protons. Although OPCs possess PAs greater than that of ammonia,
NH$_4^+$ signals are still seen in the drift time spectrum, at ppb levels [12-13]. At 2 ppm OPC, hydronium reactant ions, as well as monomer (OPC)H$^+(\text{H}_2\text{O})_n$ and dimer (OPC)$_2$H$^+(\text{H}_2\text{O})_n$ products are characterised in the drift time spectrum. The addition of ammonia results in three additional peaks: the hydrated monomer (NH$_4^+$), and monomer and dimer complexes with OPC (Figure 2.16).

![Drift Time Spectrum](image)

**Figure 2.16** Schematic representation of drift time spectra for the detection of ammonia with carrier gas doped with OPC. Adapted from Puton et al [12].

Quantitative measurements were based upon the OPC complexes. Even better detection limits for ammonia of ~5 ppb were afforded when dimethyl methanephosphonate dopant was used for environmental monitoring in air in Florida [137]. In another study, ethylene ionisation suppression was achieved using nonanone to produce more sensitive ammonia signals [157]. Sensitivity using this method was poorer, in the order of 1 ppm, as nonanone was found to compete with ammonia for proton transfer.

Nonanone has proven to be a more suitable dopant for the monitoring of hypergolic fuels as rocket propellants in spacecrafts [158]. Hydrazine (HZ) and monohydrazine (MHZ) fuels require real time, sensitive monitoring due to potential health risks at as
low as 10 ppb. The presence of volatile organic compounds (VOCs) in the atmosphere desensitised HZ and MHZ detection, and thus required dopant chemistry to remove VOC interferences. Acetone proved an ineffective chemistry, due to the lack of drift time resolution between innate reactant ion peaks for ammonia and products generated by HZ and MHZ.

The addition of 5-nonanone dopant at around 1 ppm led to single ketone ion clusters, 5-Non·AH⁺ and a ketone ion cluster with two neutrals, (5-Non)₂·AH⁺ (where A is a molecule of ammonia) [158]. These complexes were spectrally resolved due their increased collisional cross-sectional areas increasing drift time over original acetone complexes. The study involved the doping of both the drift and carrier gas in IMS, and in both instances the drift times of HZ and MHZ ions were strongly dependent upon the concentration of dopant. The multiple changes in the number of ketone molecules attached to the nitrogen base, AH⁺, during ion movement through the drift tube was explained for this dependence. It was shown that when 5-nonanone was used as a drift gas dopant, the drift times of ammonia, HZ and MHZ increased with decreasing mass of the molecule that had formed the ion [158]. This relationship resulted from the number of ketone molecule attachments to the ion core, and was equal to the number of hydrogen atoms bound to the protonated nitrogen (Figure 2.17). Complexes built on the foundations of smaller-core ion groups, e.g. ammonia had greater dimensions and cross-sectional areas than larger-core HZ and MHZ ions, and consequently longer drift times [158]. This work highlights the complexities of ion formation in mobility spectrometry.
Figure 2.17 A comparison of the ionic structures of dimethylhydrazine (DHZ) and ammonia with ketone dopants [158]. Ammonia has a longer drift time than DHZ in IMS due to a higher collisional cross-section, as four ketone molecules attach to the ion core.

The most recent advancements in dopant studies have involved chiral resolution of biological enantiomers through the use of optically-active drift gas modifiers. Dwivedi et al. [136] were the first to demonstrate this possibility by infusing enantiomerically pure 2-butanol in a N₂ drift gas to separate racemic mixtures of atenolol, serine, methionine, threonine, methyl α-glucopyranoside, glucose, penicillamine, valinol, phenylalanine and tryptophan. 0 – 65 μL h⁻¹ 2-butanol (corresponding to 0 – 14.3 ppm) was infused into the drift gas using a syringe pump to observe the effects of modifier concentration on enantiomeric resolution. Chiral separation was enabled at modifier concentrations beyond 25 μL h⁻¹ with methionine, and all compounds were separated over the modifier concentration range studied [136]. Of particular interest to the work was the differing drift time behaviour of methionine observed when the (R)-(−) and (S)-(+) forms of 2-butanol were infused. Under influxes of (R)-(−)-2-butanol, the L-form of methionine was found to have the quicker drift time, while the D-form was shown to possess a higher mobility under (S)-(+)2-butanol. The reasons for these observations were unclear, and no modelling of the analyte / modifier interactions was attempted [136]. This still remains the only recorded study of chiral separations in IMS on the basis of long-range interaction potentials without the need of a complexing agent or cluster.
Fernández-Maestre et al. [29] have recently used the work of Dwivedi et al. to investigate in greater depth the interactions of 2-butanol as a drift gas modifier with the same compounds used in the previous study. Their aim was to determine the product ions for these compounds by hyphenating with a single quadrupole mass spectrometer. The introduction of 0.17 – 0.75 μL min⁻¹ 2-butanol was shown to decrease the product ion mobilities in a non-uniform manner, due to the formation of transient 2-butanol clusters. The degree of clustering was related to the steric properties and molecular weight of the analyte. The change in reduced mobility (ΔK₀) for smaller molecules such as valinol (mr = 103.16) was greater than for larger compounds as clustering with 2-butanol affected more the relative collisional cross-section of the ion.

### 2.5.7 Negative polarity dopants in IMS

The manipulation of electron capture processes by doping with electronegative species has been successfully applied in various studies to increase product ion stability and sensitivity, (Table 2.4).
Table 2.4  A summary of negative-polarity dopants used in IMS applications.

<table>
<thead>
<tr>
<th>Detected analytes</th>
<th>Dopant</th>
<th>Introduction method and concentration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explosives including nitrotoluene derivatives.</td>
<td>Methylene chloride and other halogeno-organic compounds.</td>
<td>Permeation and diffusion source methods, including a double-stage dynamic dilution process using different air streams to deliver between 0.5 – 1000 ppt of dopant. Carbon tetrachloride used as the permeation source reservoir for generating Cl⁻ reactant ions.</td>
<td>22,159-160</td>
</tr>
<tr>
<td>5 nitrotoluene derivatives.</td>
<td>Dichloromethane for Cl⁻ and methyl bromide for Br⁻ reactant ions.</td>
<td>Cl⁻ reactant ions produced from a permeation source of methylene chloride, providing a carrier gas concentration of 35 ng cm⁻³. Methyl bromide permeation source for Br⁻, providing 20 ng cm⁻³ to the carrier gas.</td>
<td>161</td>
</tr>
<tr>
<td>Toluene and phenol-based explosives.</td>
<td>Methylene, bromine chloride and other halogeno-alkanes.</td>
<td>Halogenated reactant ions generated from permeation source methods. Single concentrations of around 1 ppm.</td>
<td>162</td>
</tr>
<tr>
<td>Halogen gases of HFI, HCI, ClO₂</td>
<td>Methyl salicylate.</td>
<td>Permeation source located in carrier gas stream. 3 – 10 ppm concentration.</td>
<td>163-164</td>
</tr>
</tbody>
</table>

The molecular ions of NO₂⁻ and NO₃⁻ are typically formed from dissociative electron attachment as fragment ions [150]. Clusters produced from these molecular ions are unstable and disintegrate during drift. Another complication is that clusters of NO₂⁻ and NO₃⁻ do not produce peaks specific to a given chemical in the drift time spectrum. The introduction and generation of strongly electronegative halide ions (EA for Cl = 349 kJ mol⁻¹) via dissociative electron capture has proven to be a more effective way of increasing product ion stability; generating more stable halide adducts. This was described in work by Proctor and Todd [152], where dichloromethane-doped carrier gas increased the selectivity of ethylene glycol dinitrate (EGDN), a principal component of dynamite. The generation of EGDN-Cl⁻ adducts were favourable to EGDN-NO₃⁻ due to the greater electron affinity of chloride. The EGDN-Cl⁻ ions were more stable in the drift tube, and only three species, Cl⁻, Cl⁻·H₂O and EGDN-Cl⁻, were detected. This induced an increase in sensitivity for the EGDN response, as all sample ionisation resulted in the formation of just one ionic species, leading to an increase in the quantity of characteristic ions reaching the detector electrode.
The generation of molecular halide ions (e.g. \( \text{Cl}_2^{-} \)) has also been reported from carrier gases containing admixtures of dichloromethane[100]. The stability of chlorine complexes in IMS have been shown to relate to the dipole alignment at the organic interface of the analyte-halide complex and the degree of C-H bonding. The increase in sensitivity of EGDN detection when using methylene chloride as a dopant has allowed for detection limits as low as 10 ppt, although the drift region must be maintained below 100 °C due to the degradation of \( \text{EGDN} \cdot \text{Cl}^{-} \) complexes at higher temperatures. A comparison of the relative ionisation processes with and without chloride dopant chemistry is shown in Figure 2.18 [12].

The rate of dissociative electron capture in the formation of halide ions is defined by the electron attachment constant (EAC) [131], and is dependent upon the electronegativity of the dopant compound, and the average electron energy, given by Equation 2.28 [12]. Values for EAC may differ by as much as 8 orders of magnitude for halogenated compounds, and thus the quantity of halogen may be estimated from its reactant ion peak area against EAC. The efficiency of ionisation is proportional to this quantity [12,164].

**Figure 2.18** Processes of explosive sample ionisation in negative mode with and without using chlorine as a reagent gas. Adapted from Puton et al [12].
\[ e^- + \text{Analyte} \rightarrow (\text{Analyte}) + Cl^- \quad \text{Equation 2.28} \]

Resolution can too be enhanced using negative ion dopants in a similar way to that described for positive ionisation. The compounds of halogen gases (HF, HCl, ClO₂) produce stable negative ions in IMS, but their mobilities overlap O₂⁻ and other reactant ion signals [12]. Methyl salicylate (MS) has been applied in such situations to produce O₂⁻ adducts with lower mobility and increased resolution [162,163].

2.5.8 Dopants for DMS

2.5.8.1 Effect of water as a dopant for DMS

An increase in humidity in the transport gas has been shown to enhance spectral resolution in DMS [165]. This effect is different to that observed in IMS applications, where increased humidity can lower the resolution in IMS spectra [9]. The quantity of average water molecules in a cluster ion, \([H_2O]_n Q^+\), is related to the concentration of water in the supportive atmosphere. Therefore under high-field conditions, the proportion of water molecules dissociated from the non-thermalised analyte ion will be greater under increased humidity. This effect can increase the alpha value (Figures 2.5 and 2.6), creating a larger differential mobility for the analyte ion, commensurate with a change in the compensation voltage required to generate a response [62]. Water can therefore act as a dopant in DMS, and may be used advantageously by spectrally resolving components that are less resolvable under lesser water concentrations [165].

It was determined from investigations with water that alpha values may be controlled according to the field-dependence of ion clusters, and therefore that modifying the drift gas chemistry could enhance ion resolution and selectivity for DMS analyses [85,91]. It has also been shown that dopants can produce product ions with little field dependence in DMS, leading to poorer detection selectivity and resolution than water chemistry [62]. A summary of the use of dopants in DMS is given in Table 2.5.

Dopant adducts with higher PAs than water (e.g. ammonia, acetone) can decrease the association of water molecules around the product ion core, accounting for lesser
degrees of clustering / declustering, and the loss of field dependence for the analyte. This was explained in a DMS study for the detection of the chemical warfare agent, tabun (GA), where in 200 ppm water chemistry, the protonated GA monomer, \( \text{GA} \cdot \text{H}^+ \cdot (\text{H}_2\text{O}) \), was associated with up to four water molecules in the low-field [87]. This quantity allowed for significant declustering at high fields, and complete spectral resolution of the analyte monomer, dimer and RIP. Upon addition of ammonia dopant at 0.1ppm, the \( \text{GA} \cdot \text{NH}_4^+ \cdot (\text{H}_2\text{O}) \) monomer only solvated with up to two water molecules, decreasing the field dependence of the monomer, and poorer resolution of the monomer and dimer product ions. Even poorer resolution was seen with acetone at 0.1 ppm, where no hydrative clustering was observed.
### Table 2.5 A summary of dopant use in DMS.

<table>
<thead>
<tr>
<th>Detected analytes</th>
<th>Dopant</th>
<th>Introduction method and concentration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabun (GA). Chemical weapon agent.</td>
<td>Water.</td>
<td>Water bubbler connected to the carrier gas stream and controlled using a mass flow controller. Generated water concentration of 10 – 1000 ppm.</td>
<td>87</td>
</tr>
<tr>
<td>Enantiomeric separation of amino acids of Trp, Arg, Phe, Met, Gln, Asn, Ile, Val, Pro and Lys and Terb.</td>
<td>Enantiomerically pure amino acid complexing agent, L-Asn.</td>
<td>Analyte complexed with chiral dopant prior to analysis.</td>
<td>166-167</td>
</tr>
<tr>
<td>Oligosaccharides of maltopentaose and maltoheptaose.</td>
<td>Methanol.</td>
<td>Methanol added as a drift gas modifier at 8000 ppm.</td>
<td>168</td>
</tr>
<tr>
<td>Five piperidine analogues and nine peptides.</td>
<td>2-propanol, 2-butanol, cyclopentanol and methanol.</td>
<td>Extraction of headspace vapours in a 5 cm³ glass vial, connected to the N₂ drift gas. Dopant concentrations: 25 – 8000 ppm.</td>
<td>169-170</td>
</tr>
<tr>
<td>Nine explosive compound vapours.</td>
<td>Methylene chloride.</td>
<td>A vapour generator was prepared using a saturated vapour source under temperature control. Mass flow regulators used to adjust dopant concentration. Exponential dilution also attempted. Concentration range: 0 – 1000 ppm.</td>
<td>171</td>
</tr>
<tr>
<td>Dimethyl methylphosphonate and butanone.</td>
<td>Benzene.</td>
<td>Dopant added to the DMS transport gas via a diffusion-based vapour generator, diluted by 0 – 300 cm³ min⁻¹ air stream. Maximum dopant concentration = 2 ppm.</td>
<td>94</td>
</tr>
<tr>
<td>m,p,o-phthalic acid isomers and four explosive isomers.</td>
<td>Methanol / water mixture.</td>
<td>Headspace of a MeOH / H₂O solution sparged and mixed with dry N₂. Added to the drift gas.</td>
<td>128</td>
</tr>
</tbody>
</table>

The detection of nine explosive vapours in the negative-polarity mode was the first such documented study of controlling alpha-parameters through the addition of organic modifiers in the drift gas [171]. Methylene chloride was introduced to clean air at 1000 ppm, using controlled vapour generation from permeation sources. The doped drift gas increased the dependence of the ion mobility upon the electric field for explosive ion by up to 6 times, increasing analytical space in the DMS spectrum. The reason for the large α-shifts was interpreted as the formation of methylene chloride cluster ions in the low-field, described by Equation 2.29, although this could
not be supported with mass spectrometry data, due to declustering at the ambient pressure/vacuum interface.

\[ M^- + C_2H_2Cl_2 \rightarrow M^- \cdot C_2H_2Cl_2 \]  \hspace{1cm} \text{Equation 2.29}

High field \hspace{1cm} Low field

The reactant ion signal intensities of CO\(_2\)-O\(_2\)\(-\cdot H_2O\), CO\(_2\)-O\(_2\)\(-\cdot and CO_3\)\(- decreased upon the addition of dopant, and the product ion signals of M\(^-\) (caused by hydride abstraction reactions) became more intense [169,170]. This indicated a more sensitive response to product ion formation with a more electronegative chemistry, in a similar way to IMS studies. Ammonia doping, at a concentration of 27 ppm, has also been applied in positive mode DMS to increase product ion sensitivity, by eliminating artefacts from solvent peak tailing [169]. More detailed studies have recently proposed modelled mechanisms for the influence of structural properties on the cluster / decluster processes [168]. Butanol, pentanol and cyclopentanol were used as N\(_2\) drift gas modifiers to investigate the molecular interactions of H-bonding and steric repulsion (hindrance) on the change in \( \alpha \)-coefficients for protein ions with varying propensities for H-bonding. The studies highlighted the following features of analyte ion mobility and possible mechanisms as shown in Table 2.6.

<table>
<thead>
<tr>
<th>Mobility Feature</th>
<th>Potential Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensation voltage shift in protein monomer response using both polar (alcohol) and non-polar (hydrocarbon) modification.</td>
<td>Electrostatic attraction between modifier and analyte altering the differential mobility behaviour of protein.</td>
</tr>
<tr>
<td>94.7 kJ mol lower global minimum energy conformation for 2-propanol/protein adduct than for the protein dimer without dopant.</td>
<td>An increase in enthalpy of formation (( \Delta H_{f} )) for the dopant-protein adduct, indicating that 2-propanol would foster more clustering than the neutral protein (&quot;core theory&quot;).</td>
</tr>
<tr>
<td>Monomer compensation voltage for sterically-hindered pentamethylpiperidine (PMP) shifted to larger negative values in presence of alcohol dopant.</td>
<td>Indicates decrease in effective cross-sectional area for the monomer in presence of dopant. A weak sterical hindrance causing dissociation of the complex in the low-field portion of the waveform (&quot;façade theory&quot;).</td>
</tr>
<tr>
<td>The smaller the size of the dopant, the greater the decrease in cross-sectional area for PMP adduct.</td>
<td>The smaller the modifier, the less steric hindrance, and greater attraction to the analyte ion.</td>
</tr>
</tbody>
</table>

Table 2.6 Influences of structural properties of protein/dopant complexes on possible cluster/decluster processes in DMS [168].
It was concluded in a later study that the alcohol modifiers competed with the H-bonds holding the protein clusters together, releasing loosely-bound peptide units and solvating the H-bonding sites [167]. This reduced the propensity for reclustering and enhanced the differential mobility separation via a reduction in the ion cross-section. Similar results were achieved in optimising for the detection of oligosaccharides by introducing methanol at a concentration of 8000 ppm into the drift gas [168].

The enantiomeric resolution of six pairs of amino acids has been achieved in DMS through prior complexation of an enantiomerically pure analyte with a chiral reference compound [166]. ESI was used as the ionisation method to introduce analytes of the form \([M'(L-Ref)_2(D/L-A)-H]^+\), where \(M'\) was a divalent metal complexation ion, A is a reference amino acid in its L-form, and is the amino acid analyte. The study proved the concept of simultaneous chiral separation of different ratios of the two enantiomers, and quantitative responses were also achieved. This work was followed by a similar study involving the enantiomeric separation of terbutaline [167]. The chiral reference amino acids were used as the effective dopants, although prior complexation still leaves DMS without a proof-of-concept study for on-line doping to provide chiral resolution.

2.5.9 Methods and limitations for introducing dopants and drift gas modifiers

The majority of current dopant methods in both academic and commercial settings employ gravimetrically calibrated permeation sources to deliver pre-determined concentrations to either the carrier or drift gas (Tables 2.1 through 2.5). Gas flow regulators such as needle valves and mass flow controllers are used to control the concentration of dopant vapours entering the spectrometer. These devices are inexpensive, durable, and provide stable chemistries in both IMS and DMS cells over several orders of magnitude. Despite these benefits, several limitations are associated with such methods. Many examples exist where the technology permits only a single concentration of dopant [4,13-14]. These devices are compound specific and optimised for only one analytical method, as product ion formation is dependent upon the chemical composition of the supporting atmosphere. In devices where gas management systems enable a range of dopant concentrations (GC for
example), the dopant chemistry is only of one type (e.g. acetone, methylene chloride). Analyses can therefore not be optimised for a range of target analytes. This becomes especially relevant when optimising the analysis for complex samples, where multiple dopants at specific concentrations are required to be delivered to the spectrometer, at pre-defined times during the course of a chromatographic run.

Current doping methodology further suffers from its incompatibility in enabling automated on/off switching between a doped and an undoped system. This is partly due to the hysteresis effects associated with using valves to control dopant concentrations from permeation sources [172], and saturation of the spectrometer from ppm concentrations of dopant [9]. Permeation sources also have limited applicability for compounds with low vapour pressures at a given temperature. Further, there is little recorded evidence of investigating dopant effects at concentrations in the ppb range. There therefore exists an analytical need and challenge to improve dopant introduction methodology in mobility spectrometry. This challenge includes introducing multiple dopants with different chemical and physical properties at varying concentrations into single mobility devices that can optimise detection characteristics for multiple target analytes. A further criterion would be a method that generated a concentration range over several orders of magnitude to enable a greater degree of ionisation control than in existing systems. Finally, if the methods for dopant introduction could be automated, this would facilitate system use with untrained personnel.

2.6 PZX dispensers for IMS

2.6.1 Background to piezoelectricity and the piezoelectric effect

Piezoelectricity is the interaction between electrical and mechanical systems, and is one of the principle physical properties of crystals, ceramics and polymers [173-174]. The application of external mechanical stress to such structures causes the development of an internal dielectric displacement, which is manifested as an internal electric polarisation, and the subsequent discharge of electricity [175-176]. The interaction process is reversible, meaning that external application of an electrical potential causes mechanical strain in the material (Figure 2.19). This interaction mechanism is termed the inverse piezoelectric effect [177]. This effect has been
routinely exploited in crystals possessing piezoelectric properties to enable the accurate, pico-litre scale ejection of matter at high velocities [178-179]. If a liquid or semi-solid substance is placed in mechanical contact with the crystal, the spatial distortion of the crystal lattice by an applied voltage causes the expulsion of a finite quantity of that substance [176]. Engineering systems have made use of this phenomenon to exploit piezoelectrically-active crystals as dispensers in commercial products for a variety of applications [180].

![Figure 2.19](image)

**Figure 2.19** The effect of applying an electrical potential to a piezoelectrically-active crystal. (1) represents the crystal at 0 potential (ground state), and (2) shows the mechanical distortion upon application of a voltage.

In crystal structures which exhibit sufficiently low symmetry to possess permanent dipole moments, the applications of either temperature or mechanical stress to the crystal induce an electric charge. The interaction processes present in these crystals are thus of three types: mechanical, thermal and electrical. Energy transfer interactions are possible between any two of these processes, and take linear relationships. Piezoelectricity is the linear interaction between electrical and mechanical systems; pyroelectricity between electrical and thermal systems [181]. The linear energy conversions in a piezoelectrically-coupled association are governed by multiple order tensors existing as extensive variables. Extensive variables describe the internal energy situation of the coupled system. The free energy, $F$, in the system is determined from the quadratic expressions accompanying these extensive variables (Equation 2.30) [181]:

$$F = \sum_{i} x_i \sum_{j} T_{ij} x_j$$
\[ F(\varepsilon, \phi) = \frac{1}{2} \alpha_{11} \varepsilon^2 + \alpha_{12} \varepsilon \phi + \frac{1}{2} \alpha_{22} \phi^2 \]  

\[ \text{Equation 2.30} \]

Where \( \varepsilon \) and \( \phi \) are extensive variables in the system, whose energy states correspond to the set of vectors that they accompany. The tensors take various orders in the piezoelectric interactions. When intensive variables connected with \( \varepsilon \) and \( \phi \) are denoted by \( E \) and \( \Phi \), a constitutive relationship exists, given by two sets of linear equations, such that \([181]\):

\[ E = \alpha_{11} \varepsilon + \alpha_{12} \phi \]  

\[ \text{Equation 2.31} \]

\[ \Phi = \alpha_{12} \varepsilon + \alpha_{22} \phi \]  

\[ \text{Equation 2.32} \]

\( E \) and \( \Phi \) may relate to the overall electrical, mechanical and thermal properties of the crystal; namely the electric field, mechanical stress and temperature respectively. \( \alpha_{11} \) and \( \alpha_{22} \) are regarded as the intrinsic primary constants for the \( (\varepsilon, \phi) \) interaction. Other interaction systems are possible between the tensors in this arrangement: \( (\varepsilon, \Phi) \), \( (E, \phi) \), \( (E, \Phi) \). Each energy relationship can be modelled by rearranging Equations 2.31 and 2.32 for the specified term. For example, the \( (E, \phi) \) relationship is determined by \([173,181]\):

\[ \frac{1}{\alpha_{11}} E - \frac{\alpha_{12}}{\alpha_{11}} \varepsilon \]  

\[ \Phi = \frac{\alpha_{12}}{\alpha_{11}} E + \left( \alpha_{22} - \frac{\alpha_{12}}{\alpha_{11}} \right) \phi \]  

\[ \text{Equations 2.33 and 2.34} \]

The extensive variables in these systems are considered the most relevant state variables for describing and determining the internal energy situation of the coupled system. Equations 2.33 and 2.34 can be related to the combined effect for the electrical and mechanical properties of a piezoelectrically-active crystal:

\[ D = \varepsilon E \]  

\[ \text{Equation 2.35} \]
Where $D$ is the electric flux density extensive variable, $\varepsilon$ is the permittivity of polarisation to the applied field, and $E$ is the applied electric field, and Hooke’s law:

$$S = sT$$  \hspace{1cm} \text{Equation 2.36}

where $S$ is the mechanical strain, $s$ is the stiffness (compliance) against the applied stress and $T$ is the mechanical stress. The linear coupling of Equations 2.35 and 2.36 can be used to describe the piezoelectric properties of the crystal, such that [173, 181]:

$$(S) = [S^E](T) + [d^T](E)$$  \hspace{1cm} \text{Equation 2.37}

$$(D) = [d](T) + [\varepsilon^T](E)$$  \hspace{1cm} \text{Equation 2.38}

where $[S^E]$ and $[\varepsilon^T]$ indicate constant electric and stress fields respectively, $[d]$ denotes the direct piezoelectric effect matrix and $[d']$ corresponds to the inverse piezoelectric effect matrix.

PZX dispensers are commonly utilised in both continuous and drop-on-demand applications. Their suitability as pico-dispensers derives from the fact that high input voltages correspond to only small spatial distortions in the crystal lattice, meaning that the size of the distortion can be varied at sub-micrometer accuracies [178, 180]. The dispensing characteristics of droplet mass (ng), velocity (m s$^{-1}$), and droplet frequency (Hz) can be optimised by configuring the driving voltage to the crystal [178, 180, 182]. The operations are relatively low-cost, consume very little of the ejected substance, and can be accomplished digitally [183]. These assets make PZX dispensers attractive prospects for analytical applications, where pico-litre quantities of dispensed material are required to change or optimise an analytical response.
2.6.2 Potential for PZX dispensers in analytical instrumentation

Recent studies have used PZX dispensers as an interface to mass spectrometers for sample deposition with electrospray ionisation sources [184] to improve detection limits for the study of biomolecules. Other studies have employed PZX dispensers to generate precise vapours from analyte solutions of explosives to calibrate and test chemical sensors [113]. The ability to use the devices to tailor a response in terms of both the dispensed mass and velocity, provides more flexible approaches for generating a range of analytical responses than with other pico-dispensers, such as nano-valves [176,185]. Additionally, responses from the excited crystals in drop-on-demand (DOD) devices are of the order of sub μ-seconds, thereby producing a potentially rapid analytical response. Hysteresis effects in DOD dispensers may or may not be as high as valve technologies [184]. Although PZX dispensers have not yet been directly interfaced to IMS systems, there has been recent interest in creating standards using PZX dispensing for calibrating IMS responses [113]. The direct interfacing of PZX dispensers to gas chromatographs as a sample introduction technology has been realised, however [16]. In this study, a DOD device was configured to a split/splitless GC injection port to deliver flexible sample masses of ethanol of between 2.24 – 44.8 nL. Linear relationships between number of applied waveforms to the crystal and signal intensity (accomplished using a flame ionisation detector) were obtained, with a relative response precision of RSD <15%. The study also proved the concept of using the dispenser to inject predetermined masses of analyte mixtures, using alkane standards. Importantly, the work demonstrated the potential benefits for using such devices to flexibly control, with high precision, responses in an analytical system.

2.7 Concluding remarks

APCI processes in IMS systems are dependent upon the chemistry of the supporting atmosphere in the spectrometer cell [9]. The supporting atmosphere may be optimised in targeted applications through the controlled introduction of a chemical dopant, either through the transport or drift gas. Dopants are introduced for the purpose of enhancing the selectivity or sensitivity of detection of target analytes. They achieve this through preferential ionisation of the analyte, whilst suppressing the potential for ionisation of matrix interferences [12]. They may also alter the
mobility coefficients of the analyte through the formation of cluster ions with different collisional cross-sections, or retarding their mobility by increasing the number of collisions in the drift gas.

This thesis focuses on a novel technique for dopant introduction in IMS systems. It is proposed that PZX pico-dispensers can be interfaced to both IMS and DMS as a means for flexible control and optimisation of dopant chemistry. Current dopant technologies based on permeation sources suffer from limitations in the range of dopant concentrations that they can administer. PZX dispensers may overcome these limitations by providing ranges of dopant concentrations of more than two orders of magnitude. The novel approach may also permit real-time switching between different dopant chemistries through drop-on-demand capabilities. The successful application of PZX dispensers as novel sample introduction systems for GC has provided weight to these hypotheses.
Chapter 3

A PZXDispenser for APCI Dopant control

3.1 Research studies

The research was undertaken in five stages:

1. Development of a methodology to optimise and evaluate PZX dispensing of IMS dopants
2. Design and development of a PZX dispenser-IMS interface for dopant control in ion mobility spectrometers
3. A proof-of-concept study demonstrating the quantitative control of dopant levels in a transverse ion mobility spectrometer with PZX dispensing
4. Monomer and dimer reactant ion peak control of APCI chemistry in DMS
5. A study in dopant modification utilising the controlled PZX dispensing of (R)-(-)-2-butanol.

This chapter describes the preparative research and development needed to create the PZX dispenser that lies at the centre of this study.

3.2 Optimisation of PZX dispensing of IMS dopants

3.2.1 Overview and objectives

The properties of the pico-dispersed droplets are determined by the physical properties of the liquids and the dynamics of mechanical stresses generated within the PZX dispenser [113,186-187]. Different liquids require different voltage waveforms to dispense a droplet of a given specification, i.e. droplet mass (ng) and droplet velocity (m s⁻¹). Important elements to this study were the optimisation of the PZX dispenser's parameters for a range of candidate IMS dopants. Control and
knowledge of the average droplet volume, $\gamma_d$, and its associated reproducibility for each liquid of interest were the main objectives of this preliminary study. The liquids used were 2-butanol, acetone, 2-nonanone, dichloromethane, 1-chlorohexane, 1-bromohexane and n-tetradecane. They were selected for their range of physical properties in terms of surface tension (mN m$^{-1}$), viscosity (g cm s$^{-1}$), boiling point (°C) and the ionisation characteristics of proton or electron affinity (kJ mol$^{-1}$). The design of the study sought to include compounds with a wide range of properties to establish if some general relationships between the control parameters, the liquids' physical characteristics and the droplets' features, were readily apparent. This part of the research addressed the following objectives:

1. Optimisation of the PZX waveforms for each dopant, using a four-factor fractional factorial central composite design approach
2. Estimation of droplet volumes of optimised droplets using microscopy and gravimetric estimates
3. Evaluations of the effect of temperature and dispensing frequency on droplet formation
4. Specification of the components needed to construct a PZX dispenser to interface to ion mobility spectrometers.

### 3.2.2 Instrumentation

A research PZX printing system, JetLab4™ (Microfab Technologies®, TX, USA) operating in the Wolfson School of Mechanical and Manufacturing Engineering at Loughborough University under the supervision of Dr. David Hutt was used for this study. Important features of this facility were integrated microscopy (200× magnification with a charge-coupled-device camera, synchronised to stroboscopic illumination of the droplets), and control of the liquid temperatures. An annotated photograph in Figure 3.1, shows a quartz crystal PZX dispenser with 60 µm orifice housed in an aluminium sheath. More detail is shown in Figure 3.2. A 3 cm$^3$ plastic luer lock reservoir (Becton Dickinson Biosciences, Oxford, UK) was attached to the dispenser, and filled with 1.5 ± 0.5 cm$^3$ of liquid. The liquid was held in the reservoir by a vacuum generated from a 100 L min$^{-1}$ rotary vacuum pump (SS Scientific Ltd., East Sussex, UK model number: W2V10) which was regulated at -0.86± 0.52 kPa (absolute). The vacuum was varied to enable the correct degree of wetting at the orifice tip. The aluminium sheath around the pico-dispenser enabled the temperature...
of the liquid reservoir to be maintained in the range 10 °C to 50 °C. Droplets were observed with a grey scale charge-coupled-device camera synchronised to stroboscopic illumination via a 625 nm red light emitting diode (LED), operating at 1200 mcd. The LED was triggered from a transistor-transistor-logic (TTL) signal from the JetDrive™ 4 waveform driver. The software application, Imagepro plus (Media Cybernetics, v. 5.1) collected the images from the camera, transmitted through a IEEE 1394 (firewire) bus to a laptop computer. The magnification of the droplets was 200×. The image capture rate was constant at 30 frames s⁻¹. More detail about the imaging systems is presented in Section 3.2.4. A \(x,y,z\) rotating arm on the JetLab™ 4 was used to position the nozzle at predetermined coordinates, and this feature was not used in these studies. The pico-dispenser orifice was also supplied with compressed air, controlled by a mass flow regulator and needle valve to deliver a purge gas of filtered air at 250 cm³ min⁻¹. The purge gas removed potential particulate contaminants or residues that would have clogged the orifice. More details of the pneumatic control to the PZX dispenser is given in Section 3.3.3.

![Annotated photograph of the JetLab™4 PZX pico-dispenser system used in this study. The dispenser here is termed “actuator” in reference to Microfab™ nomenclature.](image-url)
Figure 3.2 Close-up annotated photograph of the PZX dispenser assembly on the JetLab™ system. The letters in the Figure represent the following system components: A = aluminium sheath used to house the liquid reservoir, B = a PVC substrate, collecting the dispensed droplets, C = an engineered gap in the aluminium sheath, for visual analysis of the liquid reservoir level, D = a locking nut for positioning the reservoir, E = a 5 mm O.D. luer-lock fitting, to connect the device to pneumatic control and F = electrical wiring for producing the driving PZX waveform.

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Mucg better to use letters and a key. It doesn’t make sense to present a close up that isn’t a close up.
The waveforms supplied to the PZX dispenser were generated using a computer controlled external driver (JetDrive™ 4, Microfab Technologies, TX, USA) and supplied to the dispenser by a firewire bus lead to the crystal head. A Dell Studio 1737 lap top (Pentium Dual Core T4200 2 GHz processor, 2 Gb memory, 32-bit Windows Vista operating system) was used to run the proprietary controlled software, JetServer™, version 4. The main screenshot of the Jetserver™ software windows graphical user interface is displayed in Figure 3.3. Bipolar waveforms were designed using the JetServer™ software, generated in the JetDrive™ voltage driver and fed to the PZX crystal. The waveform frequency, $\omega$/Hz, of the bipolar voltage pulse and the number of pulses could also be controlled from 1 Hz - 2 kHz, and form a single drop to continuous operation. These control elements were used extensively throughout the entire project (see Sections 4.2 and 4.3).

![Figure 3.3 Screenshot of the main window of the JetServer™ software. The software uses bipolar waveforms which are diagrammatically represented at the foot of the screenshot. The waveform variables are shown to the top left of the screenshot, and were all inputted manually. Stroboscopic illumination of the droplets was controlled through imparting a strobe delay to the LED. The strobe delay commands are located towards the bottom left of the screenshot.](image-url)
3.2.3 The bipolar PZX waveform

The bipolar waveforms used for these studies were defined by seven continuous variables, Table 3.1. Beginning at an isoelectric point (0 V), a positive-polarity wave was applied to the crystal for a predefined time period, before a negative-polarity wave, termed an echo wave, was employed. A schematic representation of a bipolar waveform is shown in Figure 3.4. The voltages applied to the crystal (dwell voltage, $V_d$, and echo voltage, $V_e$) and the time held under these voltages (dwell time, $t_d$, and echo time, $t_e$) affect the characteristics of the dispensation process, including $\gamma_d$ and the relative precision of $\gamma_d$ (Section 3.2.5.2). Four of these seven variables, $V_d$, $V_e$, $t_d$, and $t_e$, were selected as the input factorial variables for the optimisation approach, using a central composite design as the optimisation model. They were chosen based on previous data obtained from droplet dispensing using bipolar waveforms [188] which demonstrated these four variables to contribute most significantly to $\gamma_d$ and droplet velocity.

### Table 3.1 The seven waveform variables for a bipolar wave, and their descriptions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rise time, $t_r$</td>
<td>The time taken for the waveform to reach a stable positive dwell voltage in the bipolar wave function.</td>
</tr>
<tr>
<td>Dwell voltage, $V_d$</td>
<td>The stable, positive-polarity portion of the bipolar waveform.</td>
</tr>
<tr>
<td>Dwell time, $t_d$</td>
<td>The time duration for the dwell voltage.</td>
</tr>
<tr>
<td>Fall time, $t_f$</td>
<td>The time taken for the conversion of a positive-to-negative polarity wave.</td>
</tr>
<tr>
<td>Echo voltage, $V_e$</td>
<td>The stable, negative-polarity portion of the bipolar waveform.</td>
</tr>
<tr>
<td>Echo dwell time, $t_e$</td>
<td>The time duration of the echo voltage.</td>
</tr>
<tr>
<td>Final rise time, $t_{fr}$</td>
<td>The time taken for the waveform to rise to the isoelectric point from the echo voltage.</td>
</tr>
</tbody>
</table>
Figure 3.4  Features of a bipolar waveform. $t_r$ is the rise time from the isoelectric point to the $V_d$, $tf$ is the fall time from the $V_d$ to the $V_e$ and $t_{fr}$ is the final rise time from $V_e$ to the isoelectric point. $A$ denotes the droplet detachment point.

3.2.4 Imaging and droplet characterisation

Images of the dispensing process were captured by synchronisation of the stroboscopic illumination to the bipolar waveform. This facility was part of the JetServer™ software (Figure 3.3). Characterisation of the droplets was possible by matching the frequencies of the LED strobe and the bipolar waveform; a strobe delay was used to generate an offset that enabled the droplets’ trajectory to be observed at different points. Figure 3.5 shows an example of a droplet of 2-butanol taken from the ImagePro™ Plus software. Reproducible PZX dispensing resulted in images of pico-dispersed droplets that appeared as still images under stroboscopic illumination. Variations in movement variations along the $y$-axis in Figure 3.5 could be observed, as could variations in the droplet volume. Prior knowledge of the distance between the dispenser head and the substrate enabled calculation of the size, and therefore the volume of the dispensed droplet. These were used to define the pico-dispensing operation by invoking the term, “relative droplet precision” ($P$) defined as,

$$P(\%) = \frac{\varphi (\mu m)}{\delta y (\mu m)} \times 100$$

Equation 3.1
where, $\varphi$ was the droplet diameter, and $\delta y$ was the movement of that droplet along the $y$-axis, in $\mu$m; Figure 3.5. Assuming that droplet was totally spherical, then an estimation of its volume, $\gamma_d$, could be found using Equation 3.2

$$\gamma_d = \frac{4}{3} \pi r^2$$  \hspace{1cm} \text{Equation 3.2}

where, $r$ was the radius of the imaged droplet, in $\mu$m. In this study, the droplet volume and relative droplet precision were used to characterise the PZX dispensing and the character of the resulting droplet. These responses were used to train the optimisation model generated from the central composite design (CCD) optimisation experiment. Droplet volume was estimated using a strobe delay of between 75 $\mu$s and 325 $\mu$s, depending on the liquid and factorial combinations of the optimisation model. The strobe delay was set to illuminate the droplet after it had travelled approximately 2 mm from the dispenser orifice (jet head).
Figure 3.5  A captured image of a single droplet of 62pL 2-butanol, at a strobe delay of 170 µsec. The PZX dispenser orifice is represented by A, S is the substrate which collects the droplet.
3.2.5 Experimental approaches

3.2.5.1 Reagents

1 cm$^3$ of 2-butanol, acetone, 2-nonanone, dichloromethane, 1-chlorohexane, 1-bromohexane and $n$-tetradecane were obtained from Sigma Aldrich (Gillingham, UK), at a purity greater than 99.5%. The physical chemistry data for these liquids under standard conditions (20 °C and 101 kPa) are shown in Table 3.2.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>$T_B$ /°C</th>
<th>$P_{V@20^\circ C}$ / kPa</th>
<th>$\mu_{@20^\circ C}$ / g cm s$^{-1}$</th>
<th>$\gamma_{@20^\circ C}$ / mN m$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-butanol</td>
<td>99</td>
<td>1.7</td>
<td>0.026</td>
<td>22.31</td>
</tr>
<tr>
<td>acetone</td>
<td>57</td>
<td>24.1</td>
<td>0.003</td>
<td>25.20</td>
</tr>
<tr>
<td>4-heptanone</td>
<td>145</td>
<td>0.7</td>
<td>0.029</td>
<td>25.98</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>40</td>
<td>46.7</td>
<td>0.004</td>
<td>26.50</td>
</tr>
<tr>
<td>1-chlorohexane</td>
<td>135</td>
<td>0.9</td>
<td>0.006</td>
<td>23.90</td>
</tr>
<tr>
<td>1-bromohexane</td>
<td>155</td>
<td>0.7</td>
<td>0.010</td>
<td>27.83</td>
</tr>
<tr>
<td>$n$-tetradecane</td>
<td>253</td>
<td>$1.5 \times 10^{-4}$</td>
<td>0.031</td>
<td>26.56</td>
</tr>
</tbody>
</table>

Each liquid was studied in turn and placed in the reservoir above the PZX orifice (Figure 3.2), and a backpressure of -0.86± 0.52 kPa (absolute) was applied for all liquids. The backpressure was imparted for the purpose of maintaining the liquid in suspension in the reservoir, so as to prevent spontaneous dispensing. Details of how the backpressure was applied to the reservoir are given in Section 3.3.3.

3.2.5.2 Central composite design approach for waveform optimisation

The experimental design adopted was a four-factor, 2-centroid point central composite design, giving a total of 27 factorial combinations. The four factors in the design model were the dwell voltage, dwell time, echo voltage and echo time of the bipolar waveform. The four variables were chosen from the seven waveform variables as the most significant factors from preliminary studies [188]. Predictive modelling of droplet formation by PZX dispensing is non-trivial for there are many other interacting and non-linear factors; for example reservoir temperature, $T_r$/°C, gas pressure, liquid pressure in the reservoir (height of liquid in the reservoir), and $\omega$ to list a few [113]. As such, it was decided not to include the other interacting
factors in the experimental design: the reservoir temperature was set at 22 °C and
\( \omega \) to 1000 Hz. The impact of these two factors on the droplet dispensation process
would be investigated in later studies (see Section 3.2.5.3). \( t_r, t_f \) and \( t_{fr} \) were all set to 0.1 µs for all optimisation experiments. Initial tests, which
studied each of the four CCD factors in an entirely randomised manner, were not part
of the CCD itself. These studies established the maximum and minimum levels that
could be used to produce a droplet response and these maximum and minimum
limits formed the star points in the CCD, and were different for each liquid. Table 3.3
represents the star points for the CCD model for each of the liquids used in this
study.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>( V_d / V )</th>
<th>( T_d / \mu s )</th>
<th>( V_e / V )</th>
<th>( T_e / \mu s )</th>
</tr>
</thead>
<tbody>
<tr>
<td>s high</td>
<td>s low</td>
<td>s high</td>
<td>s low</td>
<td>s high</td>
</tr>
<tr>
<td>2-butanol</td>
<td>32.0</td>
<td>17.0</td>
<td>18.0</td>
<td>10.0</td>
</tr>
<tr>
<td>acetone</td>
<td>24.0</td>
<td>17.0</td>
<td>22.5</td>
<td>16.5</td>
</tr>
<tr>
<td>4-heptanone</td>
<td>29.0</td>
<td>18.0</td>
<td>20.0</td>
<td>12.0</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>27.5</td>
<td>17.5</td>
<td>22.0</td>
<td>17.5</td>
</tr>
<tr>
<td>1-chlorohexane</td>
<td>28.0</td>
<td>15.0</td>
<td>18.0</td>
<td>10.0</td>
</tr>
<tr>
<td>1-bromohexane</td>
<td>24.0</td>
<td>16.0</td>
<td>24.0</td>
<td>14.0</td>
</tr>
<tr>
<td>n-tetradecane</td>
<td>28.0</td>
<td>21.0</td>
<td>20.0</td>
<td>12.0</td>
</tr>
</tbody>
</table>

The advantage of the CCD approach was to reduce the number of possible
experiments to a manageable quantity that would not have been possible with full-
factorial experimental models. The optimisation protocol used the Microsoft® Excel
2003 add-in, Design of Experiments PRO™ (DOE Pro), purchased from Sigma Zone
(www.sigmazone.com) to process the experimental data. The relative droplet volume
precision (Equations 3.1 and 3.2) formed the output data to the experimental model.
Each factorial combination was selected entirely at random and each level in the
design performed in triplicate for estimates of uncertainty in the model. Individual
levels were run for a total of 30 seconds to ensure the robustness of the dispensing
methods.
3.2.5.3 Gravimetric characterisation of droplets and the effect of temperature

Accurate knowledge of droplet volume was essential because the future calibration of dopants in ion mobility systems required this information. Using optimised waveforms, the liquids were dispensed into pre-weighed 2 cm³ clear glass vials (Chromacol, Herts, UK) at \( \omega = 500\text{Hz}, 1\text{KHz} \) and \( 2\text{KHz} \) for 300 s. A command programme was written to enable the JetServer™ software to run unattended under automated control and so minimise random errors. In addition, at each dispensing frequency, the liquid reservoir temperature was set to 22 °C, 25 °C and 30 °C. The temperature was allowed to stabilise for 5 min at each temperature setting and each experiment was run five times, thus creating a total set of 45 experiments for each liquid. The vials were weighed using an electronic balance, Ohaus Discovery, (Thetford, UK) model DV-215CD with 0.01 mg resolution. The vials were immediately capped after the dispensing process with a crimped silicon vial cap, and weighing was carried out no later than 15 minutes after crimping. The mean individual droplet volume, \( \gamma_d \), was determined by Equation 3.3

\[
\gamma_d = \frac{\Delta m}{N_w \rho}
\]  

Equation 3.3

Where \( \Delta m \) was the mass change, in \( \mu g \), after dispensing, \( N_w \) was the total number of waveforms and \( \rho \) was the molecular density of the dispensed liquid, in g cm³. The precision of droplet volumes using the gravimetric method was calculated as the relative standard deviations in mean weight per droplet, \( m/d(\mu g) \), from the quintuple data sets per experiment. The relationships, \( \omega \) vs \( \gamma_d \), \( \omega \) vs \( m/d \), \( T_r \) vs \( \gamma_d \) and \( T_r \) vs \( m/d \) were also determined. The results from this study are presented in Section 5.1.
3.3 Design and construction of a PZX-IMS interface

3.3.1 Overview and objectives

The process for constructing and commissioning a PZX dispenser for IMS took place in two stages:

1. the development of the PZX dispenser, and
2. the design, construction and validation of an interface between the PZX dispenser and the ion mobility spectrometer.

The first stage was based on the results and experience gained from the optimisation study (Section 3.2) using the commercially-available system. Once operation of the PZX dispenser was validated against the data from the optimisation study, the second stage involved the creation of an interface that enabled control of dopant vapour concentrations from ca. 20 – 200 µg m⁻³ for a transverse ion mobility spectrometer and a differential mobility spectrometer. The concept of the system was to generate and dispense known masses of dopant droplets through the interface which would then be volatilised and transported through a carrier gas stream. Gas phase concentrations in the ionisation region of the spectrometers were to be maintained through control of gas flows in the PZX dispenser and ω.

3.3.2 PZX dispenser design criteria

The design requirements for the PZX dispenser were:

1. PZX dispensing under software control
2. A vacuum regulation system to maintain backpressure to the liquid reservoir of -0.86± 0.52 kPa (absolute)
3. A purge gas air supply to the liquid reservoir of 20.00 ± 5.00 kPa (absolute)
4. "Real-time" stroboscopically illuminated microscopy of the PZX dispensing processes.
Pressure control was a crucial element of the design. The backpressure ensured that the meniscus of the liquid was held in suspension at the orifice tip, and prevented spontaneous dispensing of liquid. The purge pressure was needed to "blow-out" particulate matter from the orifice; environmental dust or evaporative deposits. Microscopy was needed to observe and demonstrate the operation of the PZX dispenser within the PZX dispenser assembly.

### 3.3.3 Dispenser assembly design

Figure 3.6 is a schematic overview of the PZX dispenser assembly, and a list of components is presented in Table 3.4. The imaging and PZX dispensing software were run from the same laptop. A 60 µm orifice PZX dispenser was held vertically by attaching it to a Perspex™ board fitted to a dual clamp stand. Waveforms to the dispenser were controlled through an external driver, JetDrive™ 3, via an IEEE firewire bus lead to the crystal head. The driver was controlled with compatible JetServer™ software run from a Dell Studio 1737 lap top (Pentium Dual Core T4200 2 GHz processor, 2 Gb memory, 32-bit Windows Vista operating system). A 3 cm³ luer lock plastic reservoir was attached to the base of the dispenser. Clear polytetrafluoroethylene (PTFE) tubing with dimensions of 0.63 cm O.D. × 40 cm (Grace Discovery Sciences, IL, USA) was fastened to the top of the reservoir using a Legris push-fit connection, creating an airtight seal to the manifold. The remainder of the pressure manifold was connected to the other end of the PTFE tubing. CAD diagrams of the pressure manifold are shown in Figures 3.7 and 3.8. The manifold was based on the approach used in the JetLab™4 device.
Figure 3.6  A schematic overview of the PZX dispenser assembly. The processing computer controls the PZX waveform, LED strobe and the collection of images through the microscope camera. P denotes the position of the pressure control apparatus to the dispenser; V is the voltage controller which applied the biopolar waveform to the PZX crystal and LED; PC is the laptop processing computer and S is the substrate onto which the droplets were dispensed.
<table>
<thead>
<tr>
<th>Component</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPU Laptop Dell Studio 1737, Pentium Dual Core T4200 2 GHz processor, 2 Gb memory, 32-bit Windows Vista operating system)</td>
<td>Dell Technologies, Bracknell, Berkshire, UK.</td>
</tr>
<tr>
<td>JetDrive™3 waveform and LED driver. Model number 18245.</td>
<td>Microfab technologies Ltd, Boston, Massachusetts, USA.</td>
</tr>
<tr>
<td>Strobe LED unit. 625 nm red LED, 1200 mcd luminescence, triggered from transistor-transistor-logic (TTL) signal from JetDrive™3 driver unit. Cable length = 50 cm.</td>
<td>Microfab technologies Ltd, Boston, Massachusetts, USA.</td>
</tr>
<tr>
<td>60 µm orifice PZX pico-dispenser with luer lock head. Part number: ML-00-64.</td>
<td>Microfab technologies Ltd, Boston, Massachusetts, USA.</td>
</tr>
<tr>
<td>0.63 cm outer diameter × 40 cm PFTE clear tubing. ¼” plastic Legris fitting to connect to 3 cm³ reservoir.</td>
<td>RS Components, Northamptonshire, UK.</td>
</tr>
<tr>
<td>Fairchild® model 16 vacuum regulator. 1700 kPa maximum supply pressure, -70 kPa vacuum pressure. ¼” NPT pipe connections. Part number: 16222L.</td>
<td>Fine Controls UK Ltd, The Wirral, UK.</td>
</tr>
<tr>
<td>Digital-display self-contained pressure sensor, rated pressure of -100 to +100 kPa. 0.2 kPa resolution. 1/8” NPT connection. Model number: AP34K.</td>
<td>Keyence UK Ltd, Milton Keynes, Buckinghamshire, UK.</td>
</tr>
<tr>
<td>Sub-miniature type 91 positive-purge regulator. 1/8” NPT port fittings. 0-414 kPa operating inlet pressure. Part number: 960-237-000.</td>
<td>Marsh-Bellofram, Europe Ltd, Nottingham, UK.</td>
</tr>
<tr>
<td>Ashcroft™ purge pressure gauge, 0-207 kPa operating pressure. 2” dial face with 1/8” NPT connections. Part number: 4005.</td>
<td>Multiplex Engineering, Chesterfield, UK.</td>
</tr>
<tr>
<td>Dino-Lite™ digital microscope. 80 x magnification, 30 fps image capture rate. 640 x 480 pixel resolution. USB 1.1 interface to laptop computer. Includes Dino-Capture™ software for recording captured images. Part number: AM211.</td>
<td>Absolute Data Services Ltd, Hemel Hempstead, Hertfordshire, UK.</td>
</tr>
</tbody>
</table>
Figure 3.7 A CAD design of the rear view of the PZX pressure manifold. The device is used to administer continuous backpressures of -0.34 kPa to -1.38 kPa to the liquid reservoir above the PZX orifice.
Figure 3.8 CAD schematic of the PZX pressure manifold system. The grey arrows show the direction of purged air flow, and the green arrows, the direction of vacuum flow under conditions used to enable droplet dispensing, i.e. to supply between -0.34 kPa to -1.38 kPa (absolute) to the liquid reservoir.

Comment [CMCLPT23]: Friday, 17 June 2011 13:36:28
This is good. you might want to include a 2-D schematic that describes the different operation conditions of the various valves.
A purified compressed air supply (2.3 bar) was connected to a metered pressure regulator (Norgren, Staffordshire, UK) with ¼” stainless steel national pipe thread (NPT) connections. The compressed air was passed through a 200 cm³ carbon sieve gas-purification column (Varian, UK. Part number: CP 1870) to remove hydrocarbon contaminants. The manifold was also connected to a rotary vane vacuum pump (Edwards, model number: RV3), purchased from Cole-Parmer, London, UK, capable of reducing the absolute pressure to 0.01 kPa. The vacuum regulator in the manifold (Table 3.4) maintained and controlled the absolute pressure conditions at the liquid reservoir, and was used to toggle between both positive and negative pressures.

Once the dispensing mode pressure was set to between -0.34 kPa and -1.38 kPa, it was monitored by a digital backpressure gauge (Figure 3.8). A purge pressure of 20.00 kPa was applied to the reservoir after use to expel all remaining liquid from the PZX dispenser and prevent the orifice from clogging. This process was also performed when the liquids in the reservoir were changed. An additional rinsing step was also included by purging the dispenser with 2-propanol (Sigma, Gillingham, UK). This was a standard operating procedure provided by the supplier [190].

2-way, 5-ported brass valves were used to switch between the dispensing and purge modes. The operating configuration for each mode is described in Figure 3.9. In the dispensing mode, both valves were in the open position, allowing transfer of flow from the inlets at Port 1 through to the exits at Port 4. In the purge mode, Port 2 in the purge valve was opened to permit the transfer of the purge gas towards Port 1. The result was a net purge pressure of 1.2 ± 0.2 kPa at the reservoir.
Figure 3.9 Schematics for the control of pressure at the PZX dispenser. Diagram A represents the gas flow movement in the dispensing mode, and diagram B in the purge mode. In the dispensing sequence, both 2-way valves are in the open position, permitting suction from the vacuum regulator to the reservoir. In the purge sequence, the purge valve is in the closed position, allowing a positive pressure flow towards the dispenser.

3.3.4 Validation of the PZX dispenser using gravimetric studies

The same gravimetric approach as described in Section 3.2.5.3 was used to validate the operation of the PZX dispenser. Running under the control of previously optimised waveforms (see Table 5.1), each liquid in the study was dispensed into pre-weighed 2 ml clear glass vials (Chromacol, Herts, UK) at $\omega = 500\text{Hz}$, 1 KHz and 2 KHz for 300 s each, in a manner analogous to that performed with the JetLab™4 system. A command script was written to automate the dispensing process. Each experiment was repeated five times. The liquid reservoir temperature was not intentionally altered during the experimentation period, but the ambient laboratory temperature was recorded during the full process, which spanned two days of analysis. The ambient laboratory temperature was recorded as $21.4 \pm 1.0 ^\circ\text{C}$ to 95% C.I. during analysis time. A backpressure of $-0.86 \pm 0.52 \text{kPa}$ was...
applied to the reservoir throughout the experimental procedure for all liquids. The vials were capped immediately after dispensing, using a crimped silicon vial cap, and weighed with an electronic balance, Ohaus Discovery, (Thetford, UK) model DV-215CD with 0.01 mg resolution. Weighing was carried out no later than 15 minutes after crimping.

3.3.5 PXZ dispenser design

3.3.5.1 Design criteria
The droplets generated by the PZX dispenser needed to reach the ion mobility cell as a homogenous gaseous mixture at a controlled and stable concentration. The following objectives were identified from these criteria:

- Efficient transfer and transport of dispensed dopants from the PZX nozzle, through the interface and into the ion mobility cell
- Efficient and rapid volatilisation of the pico-dispensed droplets
- Suppression of memory effects
- Control of dopant concentration
- Suppression of possible contamination from the outgassing of interface components and from environmental contact
- Electrical and thermal insulation of the dispenser from the interface components.

3.3.5.2 Interface design and functionality
A 2-dimensional schematic of the PZX dispenser developed for this study is shown in Figure 3.10. Purified compressed air was used to transport the dispensed dopants through the interface manifold. The air was cleaned with an activated carbon bed (Varian, UK. Part number CP 1870) to remove potential organic contamination. Table 3.5 summarises the features of the interface design.
Figure 3.10 Design schematic of the PZX-IMS interface that was designed and constructed for this study. F₁, F₂, F₃, and F₄ relate represent the inlet flow, exhaust flow, split flow and outlet capillary flow through the PZX-IMS manifold.
Dopants were dispensed from the PZX dispenser (A) through a 2 mm I.D. × 92 mm glass injection liner (B). The liner was purchased from Fluka, Gillingham, UK. The PZX dispenser and liner were fitted to a machined polytetrafluoroethylene (PTFE) manifold (C) with a 1 mm gap between them. The dispenser was positioned into a 4 mm orifice at the top of the PTFE manifold. The engineering specifications for the PTFE manifold are displayed in Figure 3.11. Vertical alignment was adjusted by M4 screw connections (D) to a perspex backing board (not shown). A Vespel B-0007 o-ring seal (E) provided an airtight connection around the injector. 100 - 250 cm³/min⁻¹ compressed air was supplied through a 1/16” male stainless steel union (F) (Swagelok, Manchester, UK), into a 1 mm channel (G) in the PTFE manifold, positioned at right angles to the dispensed droplets. This air flow created a curtain gas across the top of the inlet of the liner. A portion of the gas flow was diverted down through the liner where it swept the injected droplets through the evaporation zone. The rest of the air supply removed any volatile impurities arising from the PZX dispenser through an exhaust line situated 0.8 mm above the crystal orifice (I), at right angles to the orifice in the interface. Another 1/16” NPT stainless steel union (J) (Swagelok, Manchester, UK) connected the exhaust line.

The proportion of the air supply directed through the liner to the evaporation zone was controlled by a 1/8” stainless steel needle valve (K). To protect the laboratory environment, a molecular sieve filter (L) was attached to the exhaust from the needle valve. The injection liner was held by the PTFE manifold through a push-fit connection into ¼” bore drilled into the bottom of the manifold to align with the PZX dispenser (M). The liner was passed through an ultra-torr ¼” stainless steel NPT union (Swagelok, Manchester, UK) (N), containing a viton™ o-ring seal (O) that ensured a gas-tight connection within the PTFE manifold. The bore of the ultra-torr fitting was ¼” throughout. The liner was passed through a stainless steel heating block (P) (Albrook Engineering, Loughborough, UK), creating an evaporation zone. The heating block was attached to the backing board with M4 screw connections (Q). A 6.5 mm O.D. stainless steel heating cartridge (RS, Herts, UK) (R) maintained the evaporation zone at an elevated temperature between 70 °C and 120 °C. A k-type (S) thermocouple (RS, Nottingham, UK) was inserted into the heating block to monitor the temperature which was regulated using a digital thermometer (also RS, Herts, UK, part no. 206-3738).

Approximately 10 mg glass wool (T) was inserted into the bore of the glass liner to provide a heated surface to ensure complete evaporation of the liquid droplets.
end of the liner protruded from the heating block to a distance of 11 mm and was fitted into a ¼” stainless steel tee-union with a PTFE ferrule (U) (Swagelok, Manchester, UK) that also supported the liner within the heating block. A 0.32 mm I.D. × 30 cm (X) deactivated silica capillary tubing (Alltech Associates, IL, USA) was passed through the tee-union into the base of the liner, creating a split. Vapours either passed into the capillary tubing or the internal space of the tee-union (W). The proportion of dopant vapour that was allowed to flow through the capillary was controlled by a ¼” stainless steel needle valve (Y). All vapours leaving the needle valve were captured with a charcoal trap (Z). A ¼” – 0.8 mm vespel reducing ferrule (α) sealed the capillary into the bottom of the tee-union. The capillary tubing transported the split vapour to the gas supply for the reaction region of the ion mobility spectrometer.

Table 3.5 Features of the interface design which address the design objectives.

<table>
<thead>
<tr>
<th>Device objective</th>
<th>Design feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficient transfer of dispensed liquid to gas manifold.</td>
<td>Close (1 mm) proximity of glass liner to PZX injector orifice. Turbulent gas flow enabling transport of liquid into liner.</td>
</tr>
<tr>
<td>Efficient vaporisation of dispensed liquid.</td>
<td>Heating block at far end of glass liner, with fully-adjustable heating to 120 °C. Turbulent air inlet flow enabled efficient mixing into gas stream at elevated temperatures.</td>
</tr>
<tr>
<td>Control of vapour concentrations.</td>
<td>Flexible control of vapour concentrations through a needle valve controlled split, post-injection liner, and through altering the effective diluent gas flow rate.</td>
</tr>
<tr>
<td>Reduction of interface contamination.</td>
<td>An exhaust valve in the PTFE interface block allowed for the removal of volatile contaminants.</td>
</tr>
<tr>
<td>Thermal and electrical insulation of dispenser from heating body.</td>
<td>PTFE interface insulates injector from heating body. Convection of heat could only pass through glass liner.</td>
</tr>
<tr>
<td>Reduction of interferences on the dispensation characteristics.</td>
<td>PTFE interface block provided electrical and thermal insulation. Compressed air flows were present around the orifice head but at low flow-rates of 100 cm³ min⁻¹ to 250 cm³ min⁻¹, and were pre-filtered to reduce gaseous contamination. Vertical alignment of dispenser in interface.</td>
</tr>
</tbody>
</table>

An annotated photograph of the PZX dispenser is shown in Figure 3.12 and a skeletal design of the interface is represented in Figure 3.13, which illustrates more clearly the relative positions of the interface components.
Figure 3.11 2-dimensional engineering drawings of the PTFE manifold, constructed for this study. The top drawing represents the front view, and the bottom drawing, the top view. All dimensions are in mm, unless stated otherwise. A = 4 mm orifice for introducing the PZX dispenser, B = orifice for introducing the glass liner, C = ¼” NPT female thread for tapping the ¼” ultra-torr union, D and E = 1/6” female thread for introducing the gas inlet and exhaust lines, respectively. F = taps for M4 screw connections to the Perspex backing board.
Figure 3.12 An annotated photograph of the PZX-IMS interface which was designed and constructed for these studies. A = PZX dispenser, B = filtered air inlet, C = exhaust, D = PTFE manifold, E = ultra-torr gas-tight union, F = aluminium heating block, G = needle valve controlling IMS dopant concentrations, H = heating cartridge and I = tee-union split.
Figure 3.13 Skeletal diagram of PZX-IMS interface, showing the exact relative positions of the interface parts. A = PTFE manifold, B = ultra-torr gas-tight union, C = aluminium heating block and D = glass liner. Dimension is in mm.
3.3.6 Calibration and validation of interface parameters

There were four compressed air controls in the PZX dispenser, see Figure 3.14. F1 was the compressed air inlet flow, F2 the exhaust flow, F3 the split flow and F4 the dispensed flow. All flow rates in the manifold were controlled with needle valves. The mass flux, \( Q \) / ng min\(^{-1}\), of dopant vapour entering the PZX interface was defined by Equation 3.4:

\[
Q = (M_i \times \omega) \times 60
\]

Equation 3.4

where \( M_i \) was the injected mass of dopant per actuation in \( \mu g \) and \( \omega \) was the dispensing frequency in Hz. The concentration of dopant exiting the glass liner after vapourisation, \( i_g / \mu g \text{ cm}^{-3} \), was calculated from \( Q \) via Equation 3.5:

\[
i_g (\mu g \text{ cm}^{-3}) = \frac{Q(\mu g \text{ min}^{-1})}{F_3 + F_4 (\text{cm}^3 \text{ min}^{-1})}
\]

Equation 3.5

The mass-flux of dopant vapour entering the gas supply to the reaction region, \( Q_{F4} \), (i.e. the mass flux through the deactivated silica capillary tubing at the base of the manifold), was defined by Equation 3.6, where the mass flux per unit time was a function of the split flow at \( F_3 \):

\[
Q_{F4}(\mu g \text{ min}^{-1}) = 60 M_i \omega \frac{F_4}{(F_3 + F_4)}
\]

Equation 3.6

\( Q_{F4} \) was used to calculate the vapour concentration at the IMS cell, \( i_{cell} \), through Equation 3.7:

\[
[i_{cell}] (\mu g \text{ cm}^{-3}) = \frac{Q_{F4}(\mu g \text{ min}^{-1})}{F_{TG} + F_4 (\text{cm}^3 \text{ min}^{-1})}
\]

Equation 3.7
where, $F_{TG}$ was the flow rate of the gas supply to the reaction region.

Figure 3.14  Schematic showing the partitioning of compressed air flows through the PZX interface. Flow rates, $F_1$ to $F_4$, were controlled in the manifold by needle valves. The spiral configurations represent the turbulent air flow through the glass liner.
In order to accurately control the dopant vapour concentrations throughout the interface, the gas flow rates at $F_2$, $F_3$ and $F_4$ required calibrating with respect to the relative positions of their needle valves. A three-factor, 2-centroid point central composite design was constructed to enable flow rate calibration. The factorial variables were $F_1$ flow rate, with star points at 100 cm$^3$ min$^{-1}$ and 250 cm$^3$ min$^{-1}$, needle valve turns at $F_2$ (exhaust) and at $F_3$ (split), with star points at 14 and 17 turns respectively. The compressed air flow rates, $F_2$, $F_3$ and $F_4$, in cm$^3$ min$^{-1}$, formed the responses to the CCD model. Each experiment was repeated in triplicate and in a randomised order. The flow rates were measured with a digital flowmeter (Varian, UK, model number 220-1170-C). The Microsoft® Excel 2003 add-in, Design of Experiments PRO™ (DOE Pro), purchased from Sigma Zone (www.sigmazone.com) was used to model the CCD data. The package was used to calculate the residuals of the predicted values for flow rate against the actual values. A regression graph was constructed to plot these residuals in order to validate the air flows through the interface, such that vapour concentrations of dopants could be reliably calculated.

Figures 3.15 and 3.16 show the residual plots generated from the CCD experiment for the exhaust flow, $F_2$, and the accumulative flows for $F_3 + F_4$ respectively.

![Regression plot of the predicted $F_2$ (exhaust) flow rate against the actual flow rate from the CCD model.](image)

$R^2 = 0.9977$

Comment [CMCLPT32]: Friday, 17 June 2011 15:36:45
Rather than use $Y$ why not use $F_2$?

Comment [CMCLPT33]: Friday, 17 June 2011 15:35:49
This is transposed. The experimental observation is plotted on the y-axis.
Figure 3.16 Regression plot of the predicted F<sub>3</sub> + F<sub>4</sub> flow rate against the actual flow rate from the CCD model.

The results from these regression analyses (R<sup>2</sup> of >0.997) suggested that the CCD model provided a satisfactory prediction of the flow rate from the needle valve settings, once the PZX dispenser was connected to the ion mobility instruments. Further, the dopant vapour concentrations could also be estimated from Equations 3.4 to 3.7 with acceptable levels of confidence.

Careful assessment of temperature was also required before the dopant experiments were attempted. This was to ensure that the dispenser was maintained within its operating specification and that temperature effects would not interfere with the conduct of the study.

Temperature studies were carried out to investigate the effect of reservoir temperature on the operation of the PZX dispenser, see Section 5.1.2. Temperature readings were taken at the top of the PTFE manifold (i.e. the point of insertion of the PZX dispenser) while the heating block temperatures were held at 10°C increments from 70 °C to 120 °C. Each temperature was stabilised for 15 minutes before the reading was made. Each measurement was performed in duplicate on separate days. A k-type thermocouple, coupled to a Fluke 51 k/j thermometer (Fluke Ltd., Norwich, UK) was used to measure the interface temperature. Table 3.6 shows the
mean recorded interface temperature with increasing heating block temperatures that were measured in this study.

Table 3.6 The mean recorded PTFE manifold temperature, $T_{int}$, at the PZX dispenser insert, with increasing aluminium heating block temperature, $T_H$.

<table>
<thead>
<tr>
<th>$T_{int}/°C$</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
<th>110</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_H/°C$</td>
<td>22.9</td>
<td>24.1</td>
<td>25.3</td>
<td>26.4</td>
<td>27.6</td>
<td>29.2</td>
</tr>
</tbody>
</table>

The final validation check was a test for contamination. All the components used to assemble the PZX dispenser were washed with HPLC grade methanol (Fisher, Loughborough, UK) and sonicated separately for 15 minutes at 30 °C, using a 3.0 dm$^3$ sonic bath (Monmouth Scientific, Somerset, UK. Part number: RK 102 CH). The same procedure was then repeated with dichloromethane, purchased from Sigma, Dorset, UK. All components were then placed in a vacuum oven at 80 °C for 10 hours. Once assembled, an air sample with no PZX dispensing was collected by obtaining a 250 cm$^3$ air sample at the $F_4$ outlet. A 85% Tenax® (poly(2,6-diphenyl-1,4-phenylene oxide) 15% charcoal thermal desorption tube (Markes International, Rhondda Cynon Taff, UK) collected the sample for 2.5 minutes at a flow rate of 100 cm$^3$ min$^{-1}$. The tube was analysed by GC-MS. The chromatographic method used a Varian™ CP-3800 gas chromatograph (model number 104829), equipped with a 95% dimethyl- 5% phenyl- polysiloxane capillary column Varian (UK). The column dimensions were 30 m in length $\times$ 0.25 mm internal diameter $\times$ 0.25 μm film thickness. Helium was used as the carrier gas, at 2.0 cm$^3$ min$^{-1}$. The column temperature programme was set at 30°C, held for 5 minutes; 80°C at 2°C/min$^{-1}$; 230°C at 15°C/min$^{-1}$; 310°C at 32°C/min$^{-1}$ held for 2 minutes.

The analytical procedure involved desorbing components from the thermal desorption tube by heating it to 250 °C for 5 minutes, using a Markes Unity 2 thermal desorption system (Markes International, Rhondda Cynon Taff, UK) and focusing them onto a 100% Tenax® cold trap. The sample was rapidly desorbed from the trap, onto the GC column, by heating to 300 °C for 1 minute. The mass spectrometric method used a Varian-4000 electron impact-source ion-trap (model no. 00653), operating in internal ionisation mode. The $m/z$ scan range was set from 40-350. The
data acquisition was in centroid mode. Figure 3.17 shows the GC chromatogram obtained.

![Figure 3.17](image)

**Figure 3.17** 250 cm³ blank air sample chromatogram of the PZX interface. The intense peak appearing at around 2 minutes is benzene, a degradation product of Tenax®; not part of the blank air sample.

The chromatogram showed no interface contamination, and no further steps were deemed necessary to identify peaks in the chromatogram by automatic methods. Instead, peak integration using the Varian 4000 workstation™ software was carried out manually using the following integration threshold parameters: peak area threshold = 10000 V s⁻¹, peak height threshold = 180 V, S/N = 3 and peak time = 0.1 minutes. The detected peaks under these integration parameters were identified by their mass spectra, by comparison to exemplar spectra using the National Institute for Science and Technology (NIST) database (version 2.0). Table 3.7 lists the integrated peaks and their qualitative identification by comparison with the most likely match, in % probability, from the NIST library. Only three peaks were identified under the integration parameters, and of these, two were minor (relative height intensity of less than 10% of the most intense response). The most intense signal, identified as benzene, is a common degradation product of Tenax [191], and would originate from the cold trap of the thermal desorption unit. This assumption was validated by running a blank sample of the cold trap. The other two detected components were
deemed as minor contaminants, and unlikely to interfere with subsequent dopant analysis.

Table 3.7 Integrated GC peaks from the blank air sample through the PZX dispenser, and their identification by comparison to the NIST database.

<table>
<thead>
<tr>
<th>Ion</th>
<th>Most intense ions / m/z</th>
<th>Identification</th>
<th>Prob / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.989</td>
<td>689633</td>
<td>benzene</td>
<td>93.2</td>
</tr>
<tr>
<td>1.411</td>
<td>173452</td>
<td>toluene</td>
<td>69.7</td>
</tr>
<tr>
<td>3.026</td>
<td>28556</td>
<td>n-nonane</td>
<td>33.1</td>
</tr>
</tbody>
</table>

3.4 Connection of the PZX dispenser to a transverse ion mobility cell

Transverse ion mobility spectrometers and differential mobility spectrometers operate at different inlet pressures and so each instrument required a different interface to the PZX dispenser. A schematic of the transverse IMS (Environics Oy, Finland) and the connection to the interface is shown in Figure 3.18. The functionality of the spectrometer is described in detail in Section 4.2 and Figure 3.18. The spectrometer operated at atmospheric pressure (101 kPa) and used an internal pump to circulate air through the instrument. The gas circuit was made from ¼” O.D. PTFE tubing. The flow rate of air in the circuit was 1300 cm³ min⁻¹. Pressure and flow rate were monitored constantly by embedded digital mass flow controllers. It was possible to connect the 0.32 mm I.D. capillary tubing from the PZX dispenser directly into this system. The capillary was fitted to a ¼” stainless steel tee-union (Swagelok, Manchester, UK), with a graphite ¼” to 0.5 mm reducing ferrule (Grace Discovery Sciences, UK). The PTFE tubing in the spectrometer was cut 15 cm from the IMS cell.
inlet to permit the insertion of the capillary from the PZX dispenser into the internal bore of the tube for a distance of 8 cm, ending 4 cm from the reaction region of the IMS cell. To complete the circuit, the other cut end of the PTFE tubing was inserted at the 90° exit of the tee-union, and sealed using a ¼” PTFE ferrule (Grace Discovery Sciences, UK).

Figure 3.18 Schematic of the transverse IMS and the method of attachment to the PZX interface. Dispensed dopant vapours were transported through 0.32 mm I.D. × 40 cm deactivated silica capillary tubing, emerging in the IMS transport gas (A) and ionised in the reaction region of the IMS cell (B). Ions were separated through the orthogonal application of an electric field (C), to the transport gas flow, and detected by parallel plate detectors (channel numbers 1-8), based on their charge state and mobility. A digital mass flow controller operated the internal air circuit loop through a fan (D). The transport gas was cleaned at the end of the cycle through 500 cm³ carbon sieve and molecular filters (E). A 100 cm³ glass reservoir (F) was placed in the transport gas stream to sample standard atmospheres of dopant in order to reliably calibrate their concentrations.
The close proximity (4 cm) of the capillary exit to the IMS cell was required to suppress hold-up and wash out in the PTFE tubing. The positioning of the capillary at and the T-union encouraged turbulent mixing of the two gas streams.

### 3.5 Connection of the PZX interface to the differential mobility spectrometer

The differential mobility spectrometer used in this study was a Sionex® micro-DMX stand-alone device, serial number Svac-V, provided by Sionex Corporation (Massachusetts, USA). A detailed description of the instrument is given in Section 4.3.1. A flow rate of 655 ± 5 cm³ min⁻¹ purified compressed air was used as the transport gas, regulated by an electronic mass flow controller. The DMS cell operated at a gas supply pressure of 108 kPa. For this reason, it was not possible to insert the interface capillary directly into the transport gas, as the increased pressure reversed the direction of flow in the capillary. To enable the transport of dopant vapours to the DMS cell, a jet pump (Albrook Engineering, Loughborough, UK), based on the Venturi effect was attached to the interface, as shown in Figure 3.19. The mass flow controller had to be removed from the DMS manifold to permit the introduction of the jet pump. To compensate for this, the transport gas was regulated in this study via a stainless steel needle valve.

The jet pump comprised two stainless steel nozzles, located 3 mm apart, housed within 4.3 cm (I.D.) × 17.0 cm stainless steel tubing. 600 ± 5 cm³ min⁻¹ filtered compressed air was supplied to the first nozzle, engineered to converge at an angle of 5°. The gas flow entered a constriction at the entrance to the second nozzle (dimensions of 3.2 cm (I.D.) × 17 cm) which opened at 30°. This created a pressure differential in the constriction, the energy for which was supplied by a pressure gradient from the primary tubing. As the compressed air moved down the pressure gradient, kinetic energy was increased, producing a partial vacuum. This vacuum was manipulated in the jet pump by positioning the 0.32 mm I.D. capillary from the PZX interface at a right angle to the constriction, producing a suction flow in the capillary. The principles of the Venturi effect and jet pumps utilising this effect are described in detail elsewhere [192-194]. A ¼" stainless steel needle valve (Swagelok, Manchester, UK) was attached to jet pump exit to control the flow rate.
through the capillary. A split ratio of 0.42 was set, enabling a stable suction flow of 5 ± 0.1 cm³ min⁻¹ and DMS transport gas flow rate of 355 ± 5 cm³ min⁻¹.

Figure 3.19  Schematic of the functionality of the jet pump interface to the DMS cell.

Key.  A: PZX dispenser; B: needle valve controlling exhaust flow; C: glass liner; D: PTFE manifold; E: Aluminium heating block; G: split flow controlled by needle valve; H: tee-union for split flow; I: inlet nozzle to jet pump; J: outlet nozzle to jet pump; K: needle valve for secondary split flow and L: 0.32 mm I.D. × 30 cm capillary to DMS transport gas. F₁, F₂, F₃ and F₄ are the flows relating to the inlet, the exhaust, the split and the capillary through the interface, respectively. F₅, F₆, F₇ and F₈ represent the jet-pump inlet flow, the outlet flow, the secondary split flow and the total DMS cell flow. The jet pump was designed by and obtained from Professor Barry Sharp and Dr. Dinesh Asogan, Department of Chemistry, Loughborough University.
Chapter 4

Experimental procedures for calibrating and controlling dopant levels in IMS

4.1 Overview and objectives

Proof of concept experiments with a transverse ion mobility spectrometer were devised to:
- study the dynamic delivery and control of dopant vapours to an IMS cell at concentrations between <20 µg m⁻³ and >200 µg m⁻³
- establish the feasibility of the control of dopant chemistries, in both positive and negative ionisation modes
- demonstrate transient (bolus dispensing) and "steady-state" (continuous frequency dispensing) dopant ionisation responses
- quantitate transient IMS responses based on integrated peak areas obtained from bolus dispensing
- apply rapid switching (<6 seconds) of APCI chemistries between a doped and an undoped (reactant ion chemistry) system
- evaluate the extent of possible memory effects associated with transporting dopants through the PZX dispenser.

2-butanol and 1-chlorohexane were used as the dopants in these studies. 2-butanol was selected for studies in the positive ionisation mode and 1-chlorohexane for the negative mode. Dopant vapour concentrations entering the IMS cell were controlled by the split ratio in the interface (Figure 3.10), the inlet flow rate, and the bipolar waveform frequency, \( \omega / \text{Hz} \). The waveforms were developed using the methodologies described in Section 3.2.5.2 [187].

A further aim of the studies was to extend the technique and methodologies to include DMS. The following objectives were targeted from this work:
- proof of concept of using the PZX dispenser to control the monomer/dimer product ion relationships, using 2-butanol as the dopant species
- demonstrating the feasibility of simultaneous control of a dopant mixture, incorporating positive and negative ion-producing dopants
- evaluating the performance of PZX dispensing in a differential mobility spectrometer with the results previously obtained for the transverse IMS studies.

The hypothesis surrounding these objectives was that the higher-resolution Svac DMS would enable full spectral resolution of monomer and dimer product ions, developed from concentration-dependent relationships. For the simultaneous control of positive and negative-mode dopant product ion responses, 2-butanol was used as the positive mode dopant, and 1-bromohexane as the negative mode dopant species.

4.2 Experimental studies with transverse IMS

4.2.1 Instrument set up

The transverse ion mobility spectrometer used in these studies was a 16-channel dual polarity transverse instrument (Environics Oy, Finland). A schematic diagram of the experimental set up in this study is shown in Figure 3.18. The instrument was a parallel plate device with a unidirectional flow of transport gas with two arrays of eight detectors, one positive and one negative, aligned orthogonally to the inlet flow enabling the simultaneous detection of positive and negative product ions [79]. The plates were separated by a distance of 0.5 mm. The total sensor length was 6 mm. The electric field (represented as C in Figure 3.18) of the spectrometer was 50 V cm$^{-1}$. The instrument used an α-radioactive source from the decay of $^{241}$Am (activity of 5.9 MBq). Ion detection worked on the principle that ions of differing mobilities were deflected into different trajectories by the transverse electric field, and this resulted in the fractionation, by mobility, of ions into the different detector channels. Different analytes generated different profiles across the mobility channels and signal processing systems similar to those used for sensor arrays were used to assign responses to different analytes [79]. The data acquisition rate was fixed at 1 scan / s. Figure 4.1 presents an example output from the device showing the response of the...
system to 2-butanol at a concentration of 6.8 ppb(v) (20.5 µg m$^{-3}$). The drift gas was recirculated purified air maintained at a flow rate of 1300 cm$^3$ min$^{-1}$ and 298 K. The pressure in the IMS cell was 101 kPa. Sensor temperature, pressure and flow rate was continuously monitored in the cell, using proprietary software. A 100 cm$^3$ glass reservoir was fitted into the recirculating gas circuit. The reservoir was used in this study to house permeation (vapour) sources of known permeation rates to calibrate the dopant responses.
Figure 4.1  A transverse IMS spectral profile of 6.8 ppb(v) 2-butanol. Responses in channels 1-2 correspond to the reactant ion peak (RIP) in the positive mode, \([\text{H}_2\text{O}]^+\), and channels 9-10, the RIP in the negative mode, \([\text{O}_2]^−\).

Spectrometric functions (cell temperature, flow rate) and data acquisition were controlled through the accompanying software package, Chempro™, version 1.02 (Environics Oy, Finland). For this study, the software was run from a Dell Studio 1737 lap top (specifications given in Table 3.4) connected to the instrument via a COM -
Port. The software displays two GUI windows: one displays the detection parameters, such as pressure, temperature and humidity, and the other displays the detector channel responses. Screenshots for these windows are shown in Figures 4.2 and 4.3. Data for these studies were recorded in .txt format, which was imported as a Microsoft® Excel .xls file type. The processing of all data in this study was carried out in Excel 2003.

Figure 4.2 Screenshot of the window in the ChemPro100 software showing the physical and electrical parameters in the transverse ion mobility cell.
Figure 4.3  A screenshot of the detector responses from the ChemPro100 software. The observed response patterns relate to water-based reactant ion chemistry arising from the IMS transport gas operating at 1300 cm$^3$min$^{-1}$ through the IMS cell.

4.2.2  Process control

Statistical process control was used to manage the experimental campaign that ran over six weeks. The mean detector channel intensities, $I / \mu A$, for each channel were established with warning ($\mu \pm 2\sigma$) and action ($\mu \pm 3\sigma$) limits determined from experimental blanks obtained in absence of the PZX-IMS interface once a day for ten consecutive days. The data were collected for 120 seconds on each occasion. Separate control charts were created for each of the 16 detector channels, and run off a designed macro. Dopant free “blanks” were also collected with the PZX dispenser attached. These data were plotted as a Shewhart chart at the start of each day during the experimental campaign. Dopant experiments were only attempted...
when the process was within the action and warning limits for every channel. An example output of the process control chart for channel 2 (positive mode) in response to a dopant-free blank run, obtained on 17th February 2010 is displayed in Figure 4.4.

![Figure 4.4](image)

Figure 4.4  Shewhart process control chart from data obtained from a dopant-free blank sample. The signal intensities represent responses from channel 2 in the positive mode. The action and warning lines are represented by red and yellow lines respectively.

### 4.2.3 Transient dopant studies for transverse IMS

1.5 cm$^3$ of 2-butanol and 25% v/v 1-chlorohexane in n-tetradecane were placed separately into the reservoir (Figure 3.12). 1-chlorohexane required the solvent carrier to stabilise its dispensation characteristics. n-tetradecane was a practical choice of solvent for 1-chlorohexane as it possesses stable dispensation properties (viscosity of 3.19 × 10$^{-3}$ g / m s$^{-1}$, surface tension of 26.56 mN m$^{-1}$ at 20 °C), has a relatively low PA (~250 kJ mol$^{-1}$) and does not produce ions in the negative mode. 2-butanol did not require a solvent carrier as it alone possesses stable dispensation properties (viscosity of 3.1 × 10$^{-3}$ g / m s$^{-1}$, surface tension of 22.54 mN m$^{-1}$ at 20 °C) [189]. Two experiments were performed for each liquid. The first sought to generate controlled transient changes in dopant levels within the instrument. This was achieved by dispensing different masses of dopant by controlling the number of
droplets dispensed into the interface. Using the optimised waveforms, the formulation was dispensed as a burst of a fixed number of droplets, operating at 1 kHz, and the resultant IMS responses integrated. The inlet flow \( F_1 \) to the interface was 150 cm\(^3\) min\(^{-1}\) throughout. \( F_3 \) was set to 25 cm\(^3\) min\(^{-1}\), and the flow rate through the capillary outlet, \( F_4 \), was 15 cm\(^3\) min\(^{-1}\). Each experiment was repeated five times. The interface heating block temperature was set to 100 °C.

PZX dispensing was started manually, with breaks of 10 s in between each dispensation to enable the instrument to recover. 5 × 20 s samples of blank data were captured at the start of the process. These were used to enable background subtraction from the dopant responses. Table 4.1 shows the mean dispensed mass, \( m_{\text{disp}} \) / ng and mass fluxes, \( Q \) / ng min\(^{-1}\), of dopant generated at each level in the transient dispensing campaign. \( Q \) could be calculated from Equation 3.8:

\[
Q = \frac{m_{\text{disp}} \times 6 (\text{ng min}^{-1})}{(F_3 + F_4) + F_5 (\text{cm}^3\text{min}^{-1})} \times 3.75
\]

where \( F_5 \) was the flow rate of the IMS transport gas. The value of 6 was used in the equation to convert to minutes, as the boluses were dispensed every 10 seconds. The value of 3.75 represents the split ratio at the interface. The transient dopant data was processed using the following methods.

1) Five dopant-free sample blanks were run on consecutive days with the PZX dispenser attached. Each blank run was sampled for 20 s, thus creating a 100 s blank data matrix.

2) A population mean, \( \mu \), and standard deviation, \( \sigma \), were calculated for the signal intensity, pA, for each of the 16 detector channels. A S/N threshold for obtaining a quantifiable response was calculated as \( \mu + (10 \times \sigma) \) for each channel and set as the limit of quantification for subsequent dopant responses.

3) The dopant transient experiments were then run against the pre-determined background thresholds. Transient signal intensities <\( \mu + (10 \times \sigma) \) were given a value of 0; signal intensities >\( \mu + (10 \times \sigma) \) were calculated by subtracting these values from the thresholds, creating background-subtracted data.

4) The peak areas \( (A_{\text{PEAK}} \text{(pA s}^{-1}) \) for the background-subtracted data sets were calculated by the sum of the corrected signal intensities over a peak, as defined in Equation 4.2:
\[ A_{\text{PEAK}}(\text{pA s}^{-1}) = \sum i_{bc} / (n^{-1}) \]  

Equation 4.2

where, \( i_{bc} \) was the signal intensity, in pA, for a given IMS channel number at a given scan, and \( n^{-1} \) was the number of scans in the peak. As the IMS scan rate was fixed at 1 scan s\(^{-1}\), the peak area could simply be converted into intensity per second. Product ion responses produced in different channels were summed to obtain a total product ion response.

Table 4.1 A summary of the dopant masses in the transverse IMS generated from bolus dispensing at a fixed number of droplets for 2-butanol and 1-chlorohexane. The number of dispensed dopant droplets is represented by \( \delta_{\text{num}} \). \( \bar{V}_{\text{dis}} \) is the mean dispensing volume per droplet burst.

<table>
<thead>
<tr>
<th>Dopant</th>
<th>( \delta_{\text{num}} )</th>
<th>( \bar{V}_{\text{dis}} / \text{pL} )</th>
<th>( \bar{m}_{\text{dis}} / \text{ng} )</th>
<th>( Q / \text{ng min}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-butanol</td>
<td>1</td>
<td>62</td>
<td>49</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>124</td>
<td>98</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>186</td>
<td>148</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>248</td>
<td>197</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>496</td>
<td>393</td>
<td>0.47</td>
</tr>
<tr>
<td>1-chlorohexane</td>
<td>1</td>
<td>24</td>
<td>21</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>48</td>
<td>42</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>96</td>
<td>84</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>240</td>
<td>211</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>384</td>
<td>338</td>
<td>0.40</td>
</tr>
</tbody>
</table>

4.2.4 Steady-state dopant studies for transverse IMS

The second set of experiments investigated the feasibility of producing “steady-state” dopant levels by dispensing at constant frequencies. Five concentration levels for each dopant were programmed to be delivered by the dispenser by varying the flow rates \( F_1 \) and \( F_3 \). \( F_1 \) was varied from 100 - 250 cm\(^3\) min\(^{-1}\) and \( F_3 \) from 0 - 112.5 cm\(^3\) min\(^{-1}\), corresponding to split ratios between 0 and 10. The flow rate at the exhaust, \( F_2 \), was maintained at 25 cm\(^3\) min\(^{-1}\). The dispensing frequencies were 1 Hz for dispensing 2-butanol, but increased to 2 Hz to obtain 1-chlorohexane concentrations above 158.7 µg m\(^{-3}\), as this dopant was diluted in the \( n \)-tetradecane carrier. Each concentration was maintained for 20 s and between each concentration level the
dispenser was switched off for 20 s to allow for baseline signals to be reached. An initial 20 s of blank data was collected before dopant dispensing, to allow background subtraction of the resulting dopant responses. Details of the instrumental parameters required to obtain each concentration of dopant are described in Table 4.2. The background corrected relative standard deviations (%) of the individual channel responses were calculated to determine the reproducibility of the steady state.

Table 4.2 Instrumental parameters required for achieving specific steady-state IMS dopant concentrations for 2-butanol and 1-chlorohexane. [D] is the dopant concentration in the IMS cell, and ω is the dispensing frequency in Hz. The waveforms required to generate the dopant concentrations are defined in Table 5.1, and the processes required to experimentally optimise these conditions are described in Section 3.2.5.2.

<table>
<thead>
<tr>
<th>Dopant</th>
<th>[D]/ppb(v)</th>
<th>[D]/µg m⁻³</th>
<th>F₁/cm² min⁻¹</th>
<th>F₂/cm² min⁻¹</th>
<th>ω/Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-butanol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.8</td>
<td>20.5</td>
<td>250.0</td>
<td>100.0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10.1</td>
<td>30.4</td>
<td>200.0</td>
<td>80.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>14.1</td>
<td>42.4</td>
<td>200.0</td>
<td>74.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>22.3</td>
<td>67.1</td>
<td>200.0</td>
<td>62.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>39.1</td>
<td>117.7</td>
<td>200.0</td>
<td>39.0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>65.3</td>
<td>196.6</td>
<td>150.0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1-chlorohexane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.6</td>
<td>27.5</td>
<td>250.0</td>
<td>73.7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>14.6</td>
<td>71.4</td>
<td>200.0</td>
<td>15.8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>21.8</td>
<td>106.8</td>
<td>200.0</td>
<td>35.6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>32.4</td>
<td>158.7</td>
<td>150.0</td>
<td>6.0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>41.5</td>
<td>203.6</td>
<td>100.0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

4.2.5 Calibration of “steady-state” dopant responses
The planned concentrations of 2-butanol and 1-chlorohexane (Table 4.2) were experimentally validated using permeation sources, placed in the 100 cm³ glass reservoir (Figure 3.18) to deliver constant levels of dopant vapour to the spectrometer. Five vapour sources were prepared for each dopant. Vapour sources were also prepared for n-tetradecane, to establish the effect of this solvent carrier on negative mode responses, which if present would have complicated the analysis of 1-chlorohexane. The sources were prepared from 2 cm³ clear glass chromatographic vials (Chromacol, Dorset, UK), capped with an assembly composed of an 8 mm diameter aluminium cap and a polytetrafluoroethylene (PTFE) membrane. A range of membrane thicknesses (0.05 mm, 0.1 mm or 0.2 mm) were used to deliver different permeation rates. The PTFE membrane was sealed into position using a PTFE washer; 0.2 mm thick (Alltech, Stamford, UK). The total permeation area was 12 mm², see Figure 4.5. The sources were conditioned at 40 °C in a conditioning oven for 8 weeks, and calibrated gravimetrically (Ohaus Discovery, Thetford, UK. model DV-215CD with 0.01 mg resolution). Every mass loss measurement was made five times. The glass reservoir was maintained at 40 °C by placing it in a stainless steel heating block. The heating block temperature was stabilised with a cartridge process heater, monitored through a digital thermometer (RS, Northants, UK, part no. 206-3738), enabled through a proprietary k-type thermocouple. Thermal contact with the reservoir was maintained by wrapping the reservoir in aluminium foil. Details of the permeation sources used in this study are shown in Tables 4.3 to 4.5.
Table 4.3 Details of permeation source vials of 2-butanol used for calibrating the dispensed 2-butanol responses in the transverse IMS instrument. $d_{mem}$ is the membrane thickness of the vial, $t_{cal}$ represents the total calibration time over which the vials were weighed. $m_{in}$ is the mean initial mass of the prepared vial, while $m_{fin}$ represents the mean final weight before analysis. The calculated permeation rate is expressed by $R$, and $[D_{IMS}]$ is the dopant IMS concentration.

<table>
<thead>
<tr>
<th>Vial ID</th>
<th>$d_{mem}$ / mm</th>
<th>$t_{cal}$ / min</th>
<th>$m_{in}$ / g</th>
<th>$m_{fin}$ / g</th>
<th>$R$ / ng min$^{-1}$</th>
<th>$[D_{IMS}]$ / ug m$^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.2</td>
<td>80612</td>
<td>2.67243</td>
<td>2.67182</td>
<td>7.54</td>
<td>5.8</td>
</tr>
<tr>
<td>B</td>
<td>0.1</td>
<td>80602</td>
<td>2.48272</td>
<td>2.47757</td>
<td>63.96</td>
<td>122.2</td>
</tr>
<tr>
<td>C</td>
<td>0.1</td>
<td>80646</td>
<td>2.68392</td>
<td>2.67851</td>
<td>67.08</td>
<td>49.2</td>
</tr>
<tr>
<td>D</td>
<td>0.1</td>
<td>80697</td>
<td>2.83331</td>
<td>2.82049</td>
<td>158.86</td>
<td>51.6</td>
</tr>
<tr>
<td>E</td>
<td>0.05</td>
<td>80592</td>
<td>2.80989</td>
<td>2.79540</td>
<td>179.79</td>
<td>138.3</td>
</tr>
</tbody>
</table>

Table 4.4 Details of permeation source vials of 1-chlorohexane used for calibrating the dispensed 1-chlorohexane responses in the transverse IMS instrument.

<table>
<thead>
<tr>
<th>Vial ID</th>
<th>$d_{mem}$ / mm</th>
<th>$t_{cal}$ / min</th>
<th>$m_{in}$ / g</th>
<th>$m_{fin}$ / g</th>
<th>$R$ / ng min$^{-1}$</th>
<th>$[D_{IMS}]$ / ug m$^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.2</td>
<td>80111</td>
<td>2.77144</td>
<td>2.77058</td>
<td>10.79</td>
<td>11.2</td>
</tr>
<tr>
<td>B</td>
<td>0.1</td>
<td>80056</td>
<td>2.78914</td>
<td>2.78797</td>
<td>14.56</td>
<td>8.3</td>
</tr>
<tr>
<td>C</td>
<td>0.1</td>
<td>80099</td>
<td>2.56289</td>
<td>2.55877</td>
<td>51.48</td>
<td>39.6</td>
</tr>
<tr>
<td>D</td>
<td>0.1</td>
<td>80087</td>
<td>2.97319</td>
<td>2.96775</td>
<td>67.99</td>
<td>52.3</td>
</tr>
<tr>
<td>E</td>
<td>0.05</td>
<td>80076</td>
<td>2.58899</td>
<td>2.57674</td>
<td>153.01</td>
<td>117.7</td>
</tr>
</tbody>
</table>

Table 4.5 Details of permeation source vials of n-tetradecane used for calibrating the dispensed n-tetradecane responses in the transverse IMS instrument.
4.2.6 Extension to common IMS dopants

The methodology developed for studies with 2-butanol and 1-chlorohexane was also applied to acetone, dichloromethane, and 4-heptanone. These were intentionally targeted due to their suitability as IMS dopants (see Section 2.5). These compounds were dispensed at constant frequencies of 1-2 Hz to generate steady-state concentrations. The inlet flow, \( F_1 \), was varied between 100 cm\(^3\) min\(^{-1}\) and 150 cm\(^3\) min\(^{-1}\), and the split flow, \( F_3 \), was set between 20 cm\(^3\) min\(^{-1}\) and 80 cm\(^3\) min\(^{-1}\). The waveforms for all dopants were dispensed under their optimised settings (see Table 5.1), determined using the CCD approach described in Section 3.2.5.2. These studies were also evaluated against permeation source-based methods. The instrumental parameters required for steady-state dopant IMS concentrations for acetone, dichloromethane and 4-heptanone are given in Table 4.6, and the corresponding details of the permeation sources are shown in Tables 4.7 to 4.9.

### Table 4.6 Instrumental parameters required for achieving specific steady-state IMS dopant concentrations for acetone, 4-heptanone and dichloromethane.

<table>
<thead>
<tr>
<th>Dopant</th>
<th>([D]/) ppb(v)</th>
<th>([D]/) µg m(^{-3})</th>
<th>(F_1) / cm(^3) min(^{-1})</th>
<th>(F_3) / cm(^3) min(^{-1})</th>
<th>(\omega)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>15.0</td>
<td>35.4</td>
<td>250.0</td>
<td>80.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>26.6</td>
<td>62.8</td>
<td>200.0</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>42.9</td>
<td>101.2</td>
<td>200.0</td>
<td>15.8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>54.6</td>
<td>128.9</td>
<td>150.0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>69.6</td>
<td>164.3</td>
<td>150.0</td>
<td>21.0</td>
<td>2</td>
</tr>
<tr>
<td>4-heptanone</td>
<td>27.0</td>
<td>125.1</td>
<td>250.0</td>
<td>100.0</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 4.7  Details of permeation source vials of acetone used for calibrating the dispensed acetone responses in the transverse IMS instrument.

<table>
<thead>
<tr>
<th>Vial ID</th>
<th>$d_{mem}$ / mm</th>
<th>$T_{cal}$ / min</th>
<th>$m_{in}$ / g</th>
<th>$m_{fin}$ / g</th>
<th>$R$ / ng min$^{-1}$</th>
<th>$[D_{IMS}]$ / ug m$^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.2</td>
<td>50402</td>
<td>2.67493</td>
<td>2.67258</td>
<td>46.67</td>
<td>35.9</td>
</tr>
<tr>
<td>B</td>
<td>0.2</td>
<td>50415</td>
<td>2.41392</td>
<td>2.40911</td>
<td>95.42</td>
<td>73.4</td>
</tr>
<tr>
<td>C</td>
<td>0.2</td>
<td>50430</td>
<td>2.31199</td>
<td>2.30970</td>
<td>45.37</td>
<td>34.9</td>
</tr>
<tr>
<td>D</td>
<td>0.1</td>
<td>50478</td>
<td>2.87320</td>
<td>2.87016</td>
<td>60.19</td>
<td>46.3</td>
</tr>
<tr>
<td>E</td>
<td>0.1</td>
<td>50498</td>
<td>2.77711</td>
<td>2.76543</td>
<td>231.27</td>
<td>177.9</td>
</tr>
</tbody>
</table>

Table 4.8  Details of permeation source vials of 4-heptanone used for calibrating the dispensed 4-heptanone responses in the transverse IMS instrument.
<table>
<thead>
<tr>
<th>Vial ID</th>
<th>$d_{mem}$ / mm</th>
<th>$T_{cal}$ / min</th>
<th>$m_{in}$ / g</th>
<th>$m_{fin}$ / g</th>
<th>$R$ / ng min$^{-1}$</th>
<th>$[D_{IMS}]$ / ug m$^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.1</td>
<td>50600</td>
<td>2.44490</td>
<td>2.44401</td>
<td>17.68</td>
<td>13.6</td>
</tr>
<tr>
<td>B</td>
<td>0.1</td>
<td>50612</td>
<td>2.51325</td>
<td>2.51262</td>
<td>12.48</td>
<td>9.6</td>
</tr>
<tr>
<td>C</td>
<td>0.1</td>
<td>50624</td>
<td>2.89938</td>
<td>2.89889</td>
<td>9.62</td>
<td>7.4</td>
</tr>
<tr>
<td>D</td>
<td>0.05</td>
<td>50603</td>
<td>2.76443</td>
<td>2.75988</td>
<td>89.83</td>
<td>69.1</td>
</tr>
<tr>
<td>E</td>
<td>0.05</td>
<td>50609</td>
<td>2.60099</td>
<td>2.59821</td>
<td>54.99</td>
<td>42.3</td>
</tr>
</tbody>
</table>

Table 4.9 Details of permeation source vials of dichloromethane used for calibrating the dispensed dichloromethane responses in the transverse IMS instrument.

<table>
<thead>
<tr>
<th>Vial ID</th>
<th>$d_{mem}$ / mm</th>
<th>$T_{cal}$ / min</th>
<th>$m_{in}$ / g</th>
<th>$m_{fin}$ / g</th>
<th>$R$ / ng min$^{-1}$</th>
<th>$[D_{IMS}]$ / ug m$^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.2</td>
<td>45233</td>
<td>2.22314</td>
<td>2.22158</td>
<td>34.58</td>
<td>26.6</td>
</tr>
<tr>
<td>B</td>
<td>0.2</td>
<td>45212</td>
<td>2.96445</td>
<td>2.96250</td>
<td>43.16</td>
<td>33.2</td>
</tr>
<tr>
<td>C</td>
<td>0.2</td>
<td>45235</td>
<td>2.43555</td>
<td>2.43213</td>
<td>75.53</td>
<td>58.1</td>
</tr>
<tr>
<td>D</td>
<td>0.1</td>
<td>45298</td>
<td>2.66332</td>
<td>2.65231</td>
<td>243.10</td>
<td>187.0</td>
</tr>
<tr>
<td>E</td>
<td>0.1</td>
<td>45199</td>
<td>2.59789</td>
<td>2.59307</td>
<td>106.60</td>
<td>82.0</td>
</tr>
</tbody>
</table>

4.3 Control of monomer and dimer chemistries in DMS

4.3.1 Functionality of the SVAC differential mobility spectrometer

The DMS used for this study was a Sionex® micro-DMX stand-alone device, model number Svac-V, provided by the Sionex Corporation, Massachusetts, USA. The ionisation source was $^{63}$Ni, with an activity of 4.0 MBq. Purified compressed air was used as the transport gas, which was filtered through a 200 cm$^3$ molecular sieve (Varian, UK. Part number: 10172) chromatographic gas clean filter and supplied at 350 cm$^3$ min$^{-1}$ (see Section 3.5 for details of the pneumatic connections). The sample inlet port to the DMS was sealed off for these tests, and the sensor temperature was maintained at 80 °C. The anode and cathode detectors were separated by a distance
of 0.5 mm, with a total sensor length of 2 cm. In the high field conditions of the RF field, the applied electric field was 200 kV cm$^{-1}$, and in the low field, 5 kV cm$^{-1}$. The instrument was run under computer control using Sionex microDMx™ Expert software, Version 2.01 run on a Dell Studio 1737 lap top (specifications given in Table 3.4) with the control and data signals transmitted using a 9-pin COM to 9-pin serial COM cable. The data were displayed principally as contour plots, with scan time or retention time, $t_r/s$, against the compensation voltage $V_c/V$. For purposes of conformity between DMS systems, $V_c/V$ was converted to compensation field ($E_c/V$ cm$^{-1}$) at the data processing stage. For a DMS cell whose electrodes are separated by 0.5 mm, $E_c = V_c \times 20$. The signal intensities were expressed on a colour scale, and an example of the data display is depicted in Figure 4.6.

Figure 4.6  Screenshot of the detector and conductivity responses from the differential mobility spectrometer. The cell temperature, transport gas flow rate and RF field are all controlled from the right panel on the screen. Temperature and pressure in the cell are dynamically monitored. The centre of the screenshot shows the spectrometric responses at a sweeping compensation voltage over scan time or retention time. The response intensity is displayed in colour.
coordinates. Retention time is used as the y-axis variable, as the DMS can be interfaced to a gas chromatograph. The screenshot shows responses in the positive ion mode generated from applying boluses of 61 ± 4 ng 2-butanol. The reactant ion peak is shown at a compensation field of -182.8 V cm⁻¹, and the 2-butanol dimer ion at -83.2 V cm⁻¹, when applying a RF field of 20 kV cm⁻¹. Note the rapid switching of chemical responses (in the order of 3-5 seconds) between the reactant and product ions.

During analysis, Vc could either be scanned against a fixed value for RF / kV cm⁻¹, or dispersion profiles could be run to scan Vc against pre-defined stepped increases in RF (normally from RF = -900 - +300 kV cm⁻¹). The scan speed in each case was 1 scan / s. Both approaches were used in these studies. The latter was used to investigate the values for the RF field that would enable dopant responses to be generated, i.e. RF fields that would permit the stable transmission of product ions through the DMS cell. A fixed value for the RF field was then selected where there was greatest response sensitivity (where sensitivity = signal intensity, I / dopant concentration, [DMS] / ng cm³) and where full spectral resolution of the reactant and product ions was obtained. Dispersion profiles were also run without dopant dispensing as blank samples. Visual inspections of the profiles were made to determine that only ions corresponding to the reactant ion peak (RIP) from [H₂O]+ chemistry were present. This process was repeated between each analysis. An example spectrum of a blank dispersion plot is shown in Figure 4.7. Data files from the Expert™ software were composed as .xls files. Data analysis was performed in Microsoft® Excel 2003.
The RF field was ramped from 10 kV cm\(^{-1}\) to 30 kV cm\(^{-1}\) using a RF step size of 0.2 kV cm\(^{-1}\). The Vc scan at each RF step was between -45 V and +15 V, corresponding to \(E_c = -900\) - +300 V cm\(^{-1}\).

4.3.2 Experimental approaches

The jet pump at the PZX interface (Figure 3.19) was configured to ensure a transport gas flow rate, \(F_8\), of 355 cm\(^3\) min\(^{-1}\), and a capillary suction flow of 5 cm\(^3\) min\(^{-1}\). The inlet flow rate to the jet pump, \(F_5\), was 600 cm\(^3\) min\(^{-1}\), and the needle valve creating the secondary split flow, \(F_7\), was set to 250 cm\(^3\) min\(^{-1}\). This second split was an essential component in the gas management system which ensured a controlled suction flow into the jet pump. 2-butanol and 1-bromohexane (both purchased from Sigma, Gillingham, UK, purity >99.0%) were dispensed individually at a continuous waveform frequency of 1 Hz, employing previously-determined optimised waveforms (see Section 3.2.5.2). 1-bromohexane was chosen as the candidate dopant in the negative mode due to the greater resolution of brominated hydrocarbons from the RIP, compared to 1-chlorohexane [195]. The interface temperature was set to 100 °C.
for both dopants. The inlet flow to the PZX interface, $F_1$, was fixed at 200 cm$^3$ min$^{-1}$ and the exhaust flow, $F_2$, to 30 cm$^3$ min$^{-1}$.

Mass fluxes, $Q$, ng min$^{-1}$, of dopant were dynamically controlled by varying the split ratio at $F_3$, producing $F_4$ flow rates between 0.8 cm$^3$ min$^{-1}$ and 96.2 cm$^3$ min$^{-1}$. Using prior knowledge of the dispensed mass per droplet, the mass flux of dopant arriving at the detector could be calculated from Equation 4.3:

$$Q = \left( \frac{\bar{m}_{inj} \times \omega}{F_3/F_4} \right) / 0.4$$  \hspace{1cm} \text{Equation 4.3}

where, $\bar{m}_{inj}$ was the average dispensed mass per droplet, in ng, $\omega$ was the frequency of the applied PZX waveform, and $F_3/F_4$ was the split ratio in the interface. 0.4 denotes the split at the second split flow ($F_7$ in Figure 3.19). Beginning at a $F_4$ flow rate of 0.8 cm$^3$ min$^{-1}$, both dopants were dispensed at increasing DMS concentrations for periods of 20 s. The reverse format was then introduced, returning to the initial $F_4$ flow of 0.8 cm$^3$ min$^{-1}$. Dopant dispensing was stopped 20 s before and after the experimental process to provide blank data. An RF field of 21.0 kV cm$^{-1}$ was applied for both dopants. These values were determined by running dispersion profiles at $Q=26.9$ ng min$^{-1}$ for 2-butanol and $Q=34.5$ ng min$^{-1}$ for 1-bromohexane and identifying the RF field that enabled full spectral resolution of product ions from the reactant ion peak.

In the next stage of experiments, a 50:50 v/v mixture of the two dopants was prepared, and dispensed using the optimised waveform that was determined for 2-butanol, at a frequency of 1 Hz. The same experimental protocols were followed as for dispensing the dopants separately. $Q$ and $[D]$ were calculated theoretically, based upon a 2-butanol-modelled droplet size. The interface parameters for enabling specific values of $Q$ and $[D]$ for the mixture are presented in Table 4.10. Ideally, the dispensing of the mixture would have been optimised, exploiting the same method as for the individual liquids (see Section 3.2). There was not enough time to undertake this procedure. The RF field selected for characterising the reactant ions generated from the mixture was also 21.0 kV cm$^{-1}$. Details for $Q$ and $[D]$, and the instrumental parameters required to generate these conditions for the two dopants are represented in Table 4.10.
Table 4.10 PZX interface parameters required for obtaining the mass fluxes and DMS dopant concentrations in these studies. Exp. denotes the experiment number, where 1 represents separate dispensations of 2-butanol, 2 represents separate dispensations of 1-bromohexane and 3, the dopant mixture. A denotes data from 2-butanol and B, from 1-bromohexane.

<table>
<thead>
<tr>
<th>Exp.</th>
<th>( Q ) / ng min(^{-1} )</th>
<th>([D]) / µg m(^{-3} )</th>
<th>( F_2 ) split ratio</th>
<th>( F_4 ) flow / cm(^3) min(^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
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<td>5.9</td>
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<td>10.9</td>
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<tr>
<td>969</td>
<td>775</td>
<td>2.8</td>
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</table>
### 4.4 Enantiomeric separation of 2-octanol using 2-butanol as a dopant

#### 4.4.1 Overview and objectives

2-butanol has been reported in previous studies as a drift gas modifier for the separation of enantiomeric species in a linear IMS drift tube [136]. The primary objective of this final study was to start a study examining the product ions in DMS generated by the enantiomers of 2-octanol; introduced into the experiment from a permeation methods. (R)-(−)-2-butanol was dispensed as the dopant into the transport gas.
4.4.2 Experimental methods

Both enantiomers of 2-octanol (Sigma, Gillingham, UK. Purity >99.0%) were prepared as vial-based permeation sources with a PTFE membrane thickness of 0.1 mm. Methods for making these sources are described in Section 4.2.5. One source was made for each enantiomeric form. Their permeation rates were calibrated over eight months at 40 °C in a conditioning oven. Weight losses were measured using an electronic balance (Ohaus Discovery, Thetford, UK. model DV-215CD with 0.01 mg resolution). A test atmosphere generator (TAG) using purified compressed air as a carrier gas was constructed to deliver 2-octanol to the DMS cell at steady-state concentrations. A schematic of the TAG design is presented in Figure 4.8. It comprised a thermostatically-controlled stainless steel housing for a 20 cm³ clear glass gas chromatographic headspace vial (Chromacol, Gillingham, UK). The rig was maintained at 40 °C. Pre-calibrated permeation sources were placed into the vial. The vial was capped with a silicon septum, and sealed with an aluminium lid. 0.53 mm I.D. stainless steel tubing (Grace Discovery Sciences, UK) was inserted to a depth of 1 cm into the septum of the sealed vial. 200 cm³ min⁻¹ of filtered compressed air was passed through the steel tube into the headspace of the vial. The near end of the tube was attached to a 1/16” stainless steel tee-union (Swagelok, Manchester, UK) via a Vespel™ reducing ferrule (Alltech, Stamford, UK). Source vapours were removed by inserting a 0.32 mm I.D. × 15 cm deactivated silica capillary (Grace Discovery Sciences, UK) into the steel tube, projecting 2 cm from the exit of the tube. A secondary tee-union was introduced to provide a split flow for the vapours, controlled with a 1/16” stainless steel needle valve (Swagelok, Manchester, UK). A further 0.32 mm I.D. silica capillary with a length of 100 cm was used to interface the TAG to the transport gas line of the DMS.
Figure 4.8 Schematic of the TAG setup used for introducing 52.8 µg m⁻³ 2-octanol to the DMS cell. 200 cm³ min⁻¹ filtered compressed air was maintained through the manifold via a 1/8” stainless steel needle valve (A), and passed through a 0.53 mm I.D. steel capillary tubing (B). The tubing was pierced through the septum of a 20 cm³ glass headspace vial (C), containing 2 cm³ permeation vials (D) of the enantiomerically pure analyte. The vial temperatures were maintained at 40 °C via a thermostatically controlled stainless steel block (E). Analyte vapours were removed to the DMS cell by a 0.32 mm I.D. deactivated silica capillary tubing (F) interposed through the stainless steel capillary. A 1/16” stainless steel tee-union (G) acted as a split to control the concentration of analyte vapour entering the DMS. A secondary 0.32 mm I.D. × 100 cm silica capillary tubing (H) was attached to the exit of the split. The flow rate through this tubing was maintained at 5 cm³ min⁻¹.

Both enantiomers of 2-octanol were inserted into the TAG to provide a stable DMS analyte concentration of 52.8 µg m⁻³ (10 ppb). The individual enantiomeric concentrations were 33.3 µg m⁻³ for the R-(-) form and 19.5 µg m⁻³ for the S-(+) enantiomer. At an RF field of 23.6 kV cm⁻¹, the alcohol monomer ion, C₈H₁₇OH H⁺
(H₂O)ₙ⁻, was present at a compensation field of -146.6 V cm⁻¹ and the dimer ion, 2C₆H₁₇OH H⁺ (H₂O)ₙ⁻, at 26.6 V cm⁻¹ in the positive ionisation mode (Figure 5.32). R-(-)-2-butanol was dispensed into the spectrometer at an initial concentration of 60.2 µg m⁻³ for 50 s, by applying a flow rate at F₄ of 2.7 cm³ min⁻¹ (16.75 needle valve turns at the F₃ split). The concentration of R(-)-2-butanol was gradually increased to a final concentration of 945.0 µg m⁻³ by increasing the F₄ flow rate to 42.1 cm³ min⁻¹ (corresponding to 6.7 needle valve turns at the F₃ split). The resulting data were processed using Microsoft® Excel 2003.
Results and Discussion

5.1 Optimisation of the PZX dispensing of IMS dopants

5.1.1 Results from CCD experiments

Figure 5.1 Features of a bipolar waveform. \( t_r \) is the rise time from the isoelectric point to the \( V_d \), \( t_f \) is the fall time from the \( V_d \) to the \( V_e \) and \( t_{fr} \) is the final rise time from \( V_e \) to the isoelectric point. A denotes droplet attachment point.

The optimised factorial combinations from the central composite design (CCD) model and the “relative droplet precision”, \( P \) (Equation 3.1) for all the liquids studied are presented in Table 5.1. \( V_d \) and \( t_d \) were the factors found to have the largest effect on \( P \) for each liquid. The contributions of \( V_e \) and \( t_e \) were smaller, ca. 15 % by comparison. The relative impacts of the bipolar waveform factors on \( P \) for 2-butanol, acetone, 4-heptanone and dichloromethane are compared in a radar plot in Figure 5.2.

Table 5.1 A summary of the optimised factorial combinations from the CCD model for dispensing liquids in this study.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>( V_d ) V</th>
<th>( t_d ) µs</th>
<th>( V_e ) V</th>
<th>( t_e ) µs</th>
<th>( \gamma_d ) / pL</th>
<th>( P\gamma_d ) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>-----------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>-----</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>2-butanol</td>
<td>30.0</td>
<td>14.0</td>
<td>-1.0</td>
<td>1.5</td>
<td>62±4</td>
<td>95.0</td>
</tr>
<tr>
<td>1-chlorohexane</td>
<td>24.0</td>
<td>12.0</td>
<td>-1.0</td>
<td>2.0</td>
<td>60±6</td>
<td>90.2</td>
</tr>
<tr>
<td>n-tetradecane</td>
<td>26.0</td>
<td>14.0</td>
<td>-2.5</td>
<td>3.0</td>
<td>66±2</td>
<td>96.1</td>
</tr>
<tr>
<td>acetone</td>
<td>18.3</td>
<td>19.5</td>
<td>-3.0</td>
<td>1.0</td>
<td>40±5</td>
<td>70.1</td>
</tr>
<tr>
<td>4-heptanone</td>
<td>20.0</td>
<td>14.2</td>
<td>-1.0</td>
<td>1.0</td>
<td>73±3</td>
<td>94.9</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>22.5</td>
<td>18.0</td>
<td>-1.0</td>
<td>3.0</td>
<td>42±5</td>
<td>76.9</td>
</tr>
<tr>
<td>1-bromohexane</td>
<td>19.1</td>
<td>20.2</td>
<td>-1.5</td>
<td>3.0</td>
<td>51±2</td>
<td>94.9</td>
</tr>
</tbody>
</table>

The relatively high response sensitivity to changes in $V_d$ and $t_d$ meant high variations in dispensing performance at different levels in the CCD design. In some instances, particularly where $t_d$ exceeded 24 µs, no droplets were observed to be formed. In practice, this situation meant obtaining the correct balance between $V_d$ and $t_d$ to enable a more precise dispensing behaviour; $V_e$ and $t_e$ were utilised principally to “fine-tune” the dispensing process.
Figure 5.2 Radar plots demonstrating the relative contribution of each waveform variable in the CCD models on the relative droplet precision.

The numbers represent the absolute coefficient of the response.
Figure 5.3 maps the model space with respect to $V_d$ and $t_d$, showing the stability of the optimised conditions and their relative effects. Varying the strobe delay to the LED enabled various stages of the dispensation process to be captured. Such images were helpful in understanding the formation process of the droplets (Figure 5.4).

Figure 5.3 Dwell time vs dwell voltage for obtaining optimal droplet precision in the CCD experiment for the dispensing of 4-heptanone. The optimal factor combinations are given in Table 5.1. This graph demonstrates the sensitivity of the droplet precision to changes in $V_d$ and $t_d$. This is an example surface model for waveform optimisation.
Figure 5.2 Captured successive images for the dispensation of 2-butanol under its optimised bipolar waveform from LED strobe delays of between 0 µs and 150 µs. The captions represent stable dispensation behaviour, with only one droplet observed. The dispensing frequency was 1kHz.
The sequence in Figure 5.4 shows stable dispensing behaviour; only one droplet is observed (i.e. the images are free from satellite droplets), dispensed vertically at 4.2 m s\(^{-1}\). Stability such as this was not observed for many factorial combinations, particularly for liquids with viscosities <0.01 g / m s\(^{-1}\) at 20 °C. For example Figure 5.5 shows dispensing of dichloromethane at a strobe delay of 80 µs. Multiple satellite droplets are observed in the image, affecting the dispensing precision. In addition, the positions of the dispensed liquid are skewed to right (not dispensed vertically from the jet head). This may be the result of electro-static forces, or perhaps air currents transporting the liquid. Physical skewing of the dispensed droplets would have been unacceptable for the purposes of this study, as the PZX interface required the liquids to be dispensed through an orifice of just 2 mm in diameter.

![Image of dichloromethane dispensing](image)

**Figure 5.5** An image of dichloromethane dispensing, observed at a LED strobe delay of 80 µs. The waveform parameters were: \( V_d = 27.5 \) V, \( t_d = 17.5 \) µs, \( V_r = -1.0 \) V, \( t_r = 3.0 \) µs. Satellite droplets are observed to the right of the image (circled), adversely affecting the droplet precision. The image represents unstable dispensation behaviour, where the calculated droplet precision, \( P \) (from Equation 3.1) was 43.4%. The dispensing frequency was 1 kHz.
A further observation of the individual data sets showed that increasing $V_d$ led to an increase in mean droplet size for all characterised liquids. This principle has been demonstrated previously, where a linear correlation between $V_d$ and droplet size was observed [188]. No discernible correlation existed between increasing mean droplet size and droplet precision. It is useful to note however, that manipulating levels for $V_d$ can be used as a rudimentary way of controlling the masses of dispensed liquid, but at a hindrance to droplet precision. As the primary objective of this part of the study was to optimise for droplet precision, such a procedure was not attempted.

Inspection of the droplet dispensing precision ($γ_d\text{RSD\%}$) under the optimised waveforms presented in Table 5.1 reveals the relationship between $P$ and the viscosity of the dispensed liquid at 20 °C, see Figure 5.6. These data highlight an important challenge, particularly with acetone and dichloromethane. Increasing the viscosity of these liquids by lowering the reservoir temperature to around 10 °C was considered for this study, but was deemed impracticable for future work and development.

Figure 5.6  Precision in droplet volume vs the liquid viscosity at 20 °C for the liquids dispensed in this study. Values represent liquids dispensed under optimised waveforms at a dispensing frequency of 1 kHz.
With more time, it may have been possible to have incorporated other factors into the CCD model to attempt to improve the operation for low viscosity liquids; in particular including the backpressure in the CCD design. Increasing the experimental design to five or six factors would have led to 27 or 45 factorial combinations, and there was not enough time to do this. The four-factor approach in this study was the basis of a rapid method for characterising and optimising dispensing behaviour for a range of organic liquids. The optimised factorial combinations enabled droplet precision of 70.1 – 96.1% for all liquids in these studies.

The column in Table 5.1 contains the 95% confidence intervals for from the three experiments run under the optimised factorial combinations. With confidence intervals below 4.8% of for liquids with viscosities >0.01 g / m s\(^{-1}\) at 20 °C it seemed acceptable to use the CCD model to predict. For liquids with viscosities <0.01 g / m s\(^{-1}\), the predictions from multiple linear regression were less reliable. Acetone, for example, had the highest variance with confidence intervals for of 12.0% for . Adoption of this approach for liquids with relatively low viscosities is difficult and will require further study.

### 5.1.2 Validation of droplet volume and reproducibility using gravimetric methods

Tables 5.2 – 5.8 summarise the data obtained from the gravimetric studies. Note that \(T_r/°C\) was varied from 22 °C and 30 °C, and \(\omega/Hz\) between 500 Hz and 2 kHz. The experimental objective was to gain a better understanding of the effect of temperature and/or frequency on the droplet volume and compare the methods for determining mean droplet volumes, . Gravimetric results at 22 °C and 1 kHz were used in the validation study; run under the optimised conditions identified from the CCD studies.
Table 5.2  Gravimetric data obtained from the droplet dispensing of 2-butanol. $\bar{m}_{in}$ is the mean initial mass of the vial and $\Delta m$ is mean mass change after the dispensing sequence.

<table>
<thead>
<tr>
<th>$T_R$ / °C</th>
<th>$\omega$ / Hz</th>
<th>$\bar{m}_{in}$ / mg</th>
<th>$\Delta m$ / mg</th>
<th>$\Delta m$</th>
<th>RSD%</th>
<th>$\gamma_d$ / pL</th>
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<tr>
<td>500</td>
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<td>7.24</td>
<td>3.35</td>
<td>59.9</td>
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<tr>
<td>22</td>
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<td>3.79</td>
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<td></td>
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<td></td>
</tr>
<tr>
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<td>1000</td>
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</tr>
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Table 5.3  Gravimetric data obtained from the droplet dispensing of 1-chlorohexane.

<table>
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<tr>
<th>$T_R$ / °C</th>
<th>$\omega$ / Hz</th>
<th>$\bar{m}_{in}$ / mg</th>
<th>$\Delta m$ / mg</th>
<th>$\Delta m$</th>
<th>RSD%</th>
<th>$\gamma_d$ / pL</th>
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<td>500</td>
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<td>2055.55</td>
<td>29.06</td>
<td>8.67</td>
<td>55.1</td>
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</tr>
<tr>
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<td>$\omega / \text{Hz}$</td>
<td>$\bar{m}_{in} / \text{mg}$</td>
<td>$\Delta m / \text{mg}$</td>
<td>$\Delta \bar{m} / \text{mg}$</td>
<td>RSD$%$</td>
<td>$\gamma_d / \text{pL}$</td>
</tr>
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<tr>
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<th>$\bar{m}_{in} / \text{mg}$</th>
<th>$\Delta m / \text{mg}$</th>
<th>$\Delta \bar{m} / \text{mg}$</th>
<th>RSD$%$</th>
<th>$\gamma_d / \text{pL}$</th>
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</thead>
<tbody>
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<td>13.22</td>
<td>55.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>2041.01</td>
<td>15.83</td>
<td>17.84</td>
<td>33.3</td>
<td></td>
</tr>
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<td>17.88</td>
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Table 5.6 Gravimetric data obtained from the droplet dispensing of 4-heptanone.

<table>
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<tr>
<th>$T_R$ / °C</th>
<th>$\omega / Hz$</th>
<th>$\tilde{m}_{in}$ / mg</th>
<th>$\Delta m$ / mg</th>
<th>$\Delta m$ / mg</th>
<th>RSD%</th>
<th>$\gamma_d / pL$</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
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<td>67.4</td>
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<tr>
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<td>1000</td>
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<td>17.21</td>
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<td>70.2</td>
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</tr>
<tr>
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<td>2057.82</td>
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</tr>
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<td>25</td>
<td>500</td>
<td>2042.22</td>
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<td>500</td>
<td>2081.24</td>
<td>9.25</td>
<td>7.23</td>
<td>75.5</td>
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</tr>
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<td>18.51</td>
<td>2.99</td>
<td>75.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>2055.23</td>
<td>19.07</td>
<td>4.43</td>
<td>38.9</td>
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</tbody>
</table>

Table 5.7 Gravimetric data obtained from the droplet dispensing of dichloromethane.

<table>
<thead>
<tr>
<th>$T_R$ / °C</th>
<th>$\omega / Hz$</th>
<th>$\tilde{m}_{in}$ / mg</th>
<th>$\Delta m$ / mg</th>
<th>$\Delta m$ / mg</th>
<th>RSD%</th>
<th>$\gamma_d / pL$</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>2049.28</td>
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<td>9.11</td>
<td>51.2</td>
<td></td>
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<tr>
<td>22</td>
<td>1000</td>
<td>2048.82</td>
<td>19.47</td>
<td>9.57</td>
<td>48.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>2090.01</td>
<td>27.21</td>
<td>10.66</td>
<td>34.1</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>500</td>
<td>2043.44</td>
<td>10.65</td>
<td>10.02</td>
<td>53.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>2018.87</td>
<td>19.67</td>
<td>11.13</td>
<td>49.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>2032.28</td>
<td>29.77</td>
<td>9.98</td>
<td>37.3</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>500</td>
<td>2041.89</td>
<td>26.37</td>
<td>14.44</td>
<td>132.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>2056.67</td>
<td>54.66</td>
<td>16.92</td>
<td>137.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>2044.44</td>
<td>47.80</td>
<td>15.03</td>
<td>59.9</td>
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</tr>
</tbody>
</table>
Table 5.8 Gravimetric data obtained from the droplet dispensing of 1-bromohexane.

<table>
<thead>
<tr>
<th>$T_R$ / °C</th>
<th>$\omega$ / Hz</th>
<th>$m_{in}$ / mg</th>
<th>$\Delta m$ / mg</th>
<th>$\Delta m$</th>
<th>RSD%</th>
<th>$\gamma_d$ / pL</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>500</td>
<td>2079.66</td>
<td>9.76</td>
<td>1.66</td>
<td>51.3</td>
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<tr>
<td></td>
<td>1000</td>
<td>2050.00</td>
<td>19.33</td>
<td>1.40</td>
<td>50.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>2034.90</td>
<td>19.49</td>
<td>0.45</td>
<td>25.6</td>
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</tr>
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<td>25</td>
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<td>10.18</td>
<td>1.22</td>
<td>53.5</td>
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</tr>
<tr>
<td></td>
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<td>2.41</td>
<td>53.5</td>
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</tr>
<tr>
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<td>2000</td>
<td>2018.93</td>
<td>19.49</td>
<td>3.02</td>
<td>25.6</td>
<td></td>
</tr>
<tr>
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<td>500</td>
<td>2037.79</td>
<td>16.63</td>
<td>5.64</td>
<td>87.4</td>
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</tr>
<tr>
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<td>2047.30</td>
<td>31.66</td>
<td>6.89</td>
<td>83.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>2051.12</td>
<td>38.06</td>
<td>3.20</td>
<td>50.0</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5.7 compares the data from the two methods for estimating droplet volume. No apparent bias for the between sample variation data (between method) and within sample variance was observed; indicating agreement between the data sets.

Figure 5.7 A comparison of optical and gravimetric data for estimating the mean droplet volumes dispensed from the PZX dispenser. The optically characterised data is represented in grey; gravimetric data in stripes.
A t-test for the comparison of the two experimental means was used to test the hypothesis that the two methods gave statistically the same results for $\gamma_d$ (Equation 5.1):

$$t = \frac{(\bar{x}_1 - \bar{x}_2)}{s \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$  \hspace{1cm} \text{Equation 5.1}

where, $x_n$ represents the sample means for the two methods, and $s$ is the sample standard deviation, itself calculated from Equation 5.2.

$$s^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{(n_1 + n_2 - 2)}$$  \hspace{1cm} \text{Equation 5.2}

The results of these t-tests are displayed in Table 5.9, where the experimentally determined t-statistics were within the t-critical value of 2.45 (for $\alpha = 0.05$). Such results confirmed the validity of a gravimetric approach for estimating droplet volumes with variability in $T_r$ /°C and $\omega / Hz$.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>$\bar{x}_1$ / pL</th>
<th>$\bar{x}_2$ / pL</th>
<th>$s_1$</th>
<th>$s_2$</th>
<th>t-stat</th>
<th>$H_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-butanol</td>
<td>62</td>
<td>62</td>
<td>4.0</td>
<td>2.3</td>
<td>0</td>
<td>Retained</td>
</tr>
<tr>
<td>1-chlorohexane</td>
<td>60</td>
<td>62</td>
<td>6.0</td>
<td>4.7</td>
<td>-0.20</td>
<td>Retained</td>
</tr>
<tr>
<td>n-tetradecane</td>
<td>66</td>
<td>69</td>
<td>3.0</td>
<td>2.5</td>
<td>-0.71</td>
<td>Retained</td>
</tr>
<tr>
<td>acetone</td>
<td>40</td>
<td>49</td>
<td>4.8</td>
<td>4.1</td>
<td>-1.23</td>
<td>Retained</td>
</tr>
<tr>
<td>4-heptanone</td>
<td>73</td>
<td>70</td>
<td>5.0</td>
<td>5.6</td>
<td>0.36</td>
<td>Retained</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>42</td>
<td>49</td>
<td>4.9</td>
<td>4.7</td>
<td>-0.92</td>
<td>Retained</td>
</tr>
<tr>
<td>1-bromohexane</td>
<td>51</td>
<td>51</td>
<td>1.8</td>
<td>0.7</td>
<td>0.08</td>
<td>Retained</td>
</tr>
</tbody>
</table>

The mean droplet volumes $\gamma_d$ of all liquids remained stable when increasing $T_r$ from 22 °C to 25 °C. A further increase of $T_r$ to 30 °C caused a rise in $\gamma_d$ to between 150% to 200% of the original $\gamma_d$ at 22 °C for all liquids with the exceptions of 4-
heptanone and \textit{n}-tetradecane. Figure 5.8 represents the mean droplet volume against an increase in reservoir temperature for all liquids dispensed at a frequency of 1 kHz. This illustrates a decrease in the viscosity of the dispensed liquid at 30 °C, causing larger boluses to be formed. It was presumed that 4-heptanone and \textit{n}-tetradecane dispensation characteristics were less affected by increasing temperature due to their relatively high viscosities (0.029 g / cm s\(^{-1}\) and 0.031 g / cm s\(^{-1}\) at 20 °C respectively) in comparison to the other liquids in this study. The effect of \(T_R\) on \(\gamma_d\) was replicated at all waveform frequencies. The data enabled an understanding of how the dispensing process would be affected in the heated PZX interface. From this data, it was determined that the point of physical contact between the PZX dispenser and the interface should not exceed 25 °C, to enable control of \(\gamma_d\) when dispensing dopants through the interface.

![Figure 5.8](image-url)

**Figure 5.8** Calculated mean droplet volume against liquid reservoir temperature for all liquids in this study. Shapes depicting droplet data values represent the following: \(\bigstar\) = dichloromethane, \(\blacksquare\) = acetone, \(\blacktriangle\) = 1-chlorohexane, \(\blacklozenge\) = 2-butanol, \(\bigcirc\) = 1-bromohexane, \(\square\) = \textit{n}-tetradecane, and \(\blacktriangleleft\) = 4-heptanone.
Figure 5.9 represents $\gamma_d$ against $\omega$ for all characterised liquids, dispensed at a reservoir temperature of 22 °C. Dispensing at 2 kHz produced $\gamma_d$ of around 50% of that when dispensed at between 500 Hz and 1 kHz. The reasons for this are yet to be experimentally determined, but may be the result of destructive interference of the waveform when applied at very high frequencies, producing fewer droplet actuations. Similar results to these have been observed in previous studies [196]. As a result of these data, it was decided that in subsequent work, with dispensing a fixed number of droplets, to apply a waveform of 1 kHz as a constant dispensing frequency.

![Graph showing $\gamma_d$ against $\omega$ for all characterised liquids](image)

Figure 5.9 Calculated mean droplet volume against waveform frequency for all liquids characterised in this study. Data point shapes represent the same dispensed liquids as in Figure 5.8.

Despite the variations of $\gamma_d$ with changes in $T_r$ and $\omega$, $\Delta m$ RSD% (Tables 5.2 – 5.8) for the quintuplet data sets were less than 8.7% for all gravimetric experiments involving 2-butanol, 1-bromohexane, 4-heptanone and $n$-tetradecane. As expected, $\gamma_d$ reproducibility for acetone, 1-chlorohexane and dichloromethane was poorer; RSDs as much as 18.22% were observed for acetone at 30 °C. These data supported the premise that optimised PZX dispensing could provide controlled dispensed masses of liquids of a variety of physical and chemical properties at the picolitre level. These studies led to understanding of the design features needed to interface PZX dispensers to analytical instrumentation.
5.2 Gravimetric validation of the PZX dispenser

The constructed PZX device was validated by comparison of gravimetric data obtained from the JetLab™4 system. Table 5.10 summarises the gravimetric data from the PZX dispenser at 22 °C; used as it most closely resembled temperature conditions in the laboratory (21.4 ± 1.0 °C).

Table 5.10 A summary of the gravimetrically calculated droplet volumes of organic liquids in this study using the purpose-built PZX dispenser. Dispensing frequency = 1 kHz.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>(\bar{m}_{in}/\text{mg})</th>
<th>(\Delta m/\text{mg})</th>
<th>(\Delta m) RSD%</th>
<th>(\gamma_d)/pL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-butanol</td>
<td>2018.93</td>
<td>14.88</td>
<td>6.37</td>
<td>61.5</td>
</tr>
<tr>
<td>1-chlorohexane</td>
<td>2032.22</td>
<td>16.98</td>
<td>10.54</td>
<td>64.4</td>
</tr>
<tr>
<td>n-tetradecane</td>
<td>2020.01</td>
<td>15.84</td>
<td>6.92</td>
<td>69.2</td>
</tr>
<tr>
<td>acetone</td>
<td>2033.92</td>
<td>10.37</td>
<td>29.06</td>
<td>43.6</td>
</tr>
<tr>
<td>4-heptanone</td>
<td>2032.89</td>
<td>17.92</td>
<td>3.94</td>
<td>73.1</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>2034.00</td>
<td>20.19</td>
<td>24.17</td>
<td>50.6</td>
</tr>
<tr>
<td>1-bromohexane</td>
<td>2033.75</td>
<td>21.31</td>
<td>3.29</td>
<td>56.0</td>
</tr>
</tbody>
</table>

The calculated precision in mass change, \(\Delta m\), of all dispensed liquids was <6.92% RSD with liquids possessing viscosities greater than 0.01 g / m s\(^{-1}\) at 25 °C. This suggests that the waveform optimisation protocol developed from previous experiments was an effective method for providing stable control of the dispensing process in different PZX dispensing systems. As expected, \(\Delta m\) was inferior for dispensing experiments involving 1-chlorohexane, dichloromethane and acetone.

The gravimetrically-determined droplet volumes for both instruments appear to closely resemble each other (\(\gamma_d\) for the purpose-built system was within ± 9% of the calculated \(\gamma_d\) for the JetLab™4 device for all liquids) suggesting experimental consistency of the two systems for providing accurate masses of dispensed liquids.

To test this hypothesis, i.e. that the two systems give statistically the same mean values for \(\gamma_d\), standard t-tests were conducted from the \(\gamma_d\) data at a frequency of 1 kHz for all liquids, using the methods in Equations 5.1 and 5.2., see Table 5.11. All results were within the critical t-value (to 8 degrees of freedom) of 2.31 to a probability of 0.05 (95%). The null hypothesis was therefore upheld in every case, implying that the two systems gave statistically equivalent values for \(\gamma_d\) to a
probability of 95%. These results provided satisfactory levels of confidence in the subsequent calculation of masses of dispensed liquids and their subsequent vapour-phase concentrations.

Table 5.11  

<table>
<thead>
<tr>
<th>Liquid</th>
<th>$\bar{x}_1$</th>
<th>$\bar{x}_2$</th>
<th>$s_1$</th>
<th>$s_2$</th>
<th>t-stat</th>
<th>$H_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-butanol</td>
<td>61.5</td>
<td>62.0</td>
<td>241.08</td>
<td>234.98</td>
<td>-0.001</td>
<td>retained</td>
</tr>
<tr>
<td>1-chlorohexane</td>
<td>64.4</td>
<td>60.0</td>
<td>437.28</td>
<td>466.59</td>
<td>0.005</td>
<td>retained</td>
</tr>
<tr>
<td>n-tetradecane</td>
<td>69.2</td>
<td>66.0</td>
<td>331.47</td>
<td>253.92</td>
<td>0.001</td>
<td>retained</td>
</tr>
<tr>
<td>acetone</td>
<td>43.6</td>
<td>40.0</td>
<td>552.41</td>
<td>406.36</td>
<td>-0.008</td>
<td>retained</td>
</tr>
<tr>
<td>4-heptanone</td>
<td>73.1</td>
<td>73.0</td>
<td>210.53</td>
<td>560.20</td>
<td>0.008</td>
<td>retained</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>50.6</td>
<td>42.0</td>
<td>618.84</td>
<td>467.02</td>
<td>0.002</td>
<td>retained</td>
</tr>
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<td>1-bromohexane</td>
<td>56.0</td>
<td>50.8</td>
<td>103.04</td>
<td>71.12</td>
<td>0.040</td>
<td>retained</td>
</tr>
</tbody>
</table>

5.3  

Calibration data from permeation sources

The calibration data obtained with the 2-butanol and 1-chlorohexane permeation sources are presented in Figures 5.10 and 5.11 respectively. See Tables 4.3 and 4.4 in Section 4.2.5 for details on methodology and permeation rates. 2-butanol generated linear responses ($R^2 = 0.983$) at channel 3 in the positive mode from concentrations of 5.8 µg m$^{-3}$ (1.9 ppb(v)) to 138.3 µg m$^{-3}$ (45.3 ppb(v)). Second and third product ion responses for 2-butanol were observed in channels 4 and 5. The limit of detection (calculated as $3\sigma$ from the mean baseline response, for the product ion in channel 4 was 8.1 µg m$^{-3}$ (2.7 ppb(v)). This response increased linearly from 51.6 µg m$^{-3}$ (17.2 ppb(v)) to 312.1 µg m$^{-3}$ (104.0 ppb(v)). The product ion signal corresponding to channel 5 increased linearly ($R^2 = 0.992$) from 51.6 µg m$^{-3}$ (17.2 ppb(v)) to 367.1 µg m$^{-3}$ (122.0 ppb(v)), which was the highest permeation source concentration used for calibration.
A concentration-response relationship could be determined from summing the background-corrected signal intensities over the detector channels which produced quantifiable responses from product ions. Summing responses from channels 3-5 generated a linear relationship ($R^2 = 0.988$) across the concentrations studied. Since smaller ion clusters with higher mobilities should theoretically be deflected more readily by the applied electric field, the product ion response at channel 3 was attributed to be most likely due to the monomer ion, $\{(H_2O)C_4H_9OH\}^+$. The responses at channels 4 and 5 were assumed to be larger, hence these were attributed to the alcohol dimer ion, $\{(H_2O)2C_4H_9OH\}^+$, or alcohol clustering with a larger number of H$_2$O molecules. The exact identity of the product ion species could not be determined using information exclusively from these transverse ion mobility spectra. A mass spectrometer interfaced to the mobility cell would have been required for confirmatory analysis, and to determine levels of hydrative clustering. Characterisation of the product ion species was not a fundamental element of this proof-of-concept study.
Figure 5.10 Transverse IMS responses obtained from permeation sources of 2-butanol. The top graph represents the background-corrected signal intensity, $I / pA$, against the individual detector channels in the positive mode with changing dopant concentration. The letters relate to the following dopant concentrations: $A = 5.8 \mu g \text{ m}^{-3}$, $B = 49.2 \mu g \text{ m}^{-3}$, $C = 100.8 \mu g \text{ m}^{-3}$, $D = 189.9 \mu g \text{ m}^{-3}$, $E = 312.1 \mu g \text{ m}^{-3}$ and $F = 367.1 \mu g \text{ m}^{-3}$. The bottom graph shows the linear relationship of the signal intensity against dopant concentration, $[D] / \mu g \text{ m}^{-3}$, for the summation of the product ion responses (channels 3-5). The graph was used to calibrate the responses from dispensed 2-butanol.
Figure 5.11  Transverse IMS responses obtained from permeation sources of 1-chlorohexane. The top graph represents the background-corrected signal intensity against the individual detector channels in the positive mode with changing dopant concentration. The letters relate to the following dopant concentrations: A = 5.3 μg m⁻³, B = 19.5 μg m⁻³, C = 39.6 μg m⁻³, D = 71.8 μg m⁻³, E = 117.7 μg m⁻³, F = 157.3 μg m⁻³ and G = 229.1 μg m⁻³. The bottom graph shows the linear relationship of the signal intensity against dopant concentration, [D] / μg m⁻³, for the product ion response in channel 11. The graph was used to calibrate the responses from dispensed 1-chlorohexane.

Permeation sources from 1-chlorohexane produced product ion responses in channels 10 and 11. Concentrations between 8.3 μg m⁻³ (1.7 ppb(v)) and 59.1 μg m⁻³
(12.1 ppb(v)) of 1-chlorohexane produced an initial product ion response in channel 10, overlapping the reactant ion response from O$_2^-$. Background subtraction from blank data sets enabled this response to be evaluated. The signal at channel 10 decreased at concentrations above 59.1 µg m$^{-3}$ (12.1 ppb(v)), as a second product ion species at channel 11 was formed. A linear relationship ($R^2 = 0.993$) between 1-chlorohexane concentration (µg m$^{-3}$) and signal intensity (pA) was observed from concentrations of 11.2 µg m$^{-3}$ (2.3 ppb(v)) to 229.1 µg m$^{-3}$ (46.9 ppb(v)), which was the highest concentration used from the constructed permeation sources. It is assumed that dissociative electron capture processes in the presence of lower halogen concentrations formed chloride ions, $\{(\text{H}_2\text{O})_n\text{Cl}\}$ in the mobility cell, leading to the presence of high mobility signals associated with channel 10 [100]. At higher concentrations of 1-chlorohexane, chloride ion adducts, $\{(\text{H}_2\text{O})_n\text{C}_6\text{H}_{13}\text{Cl}\}$ were proposed, creating product ions with lower mobilities that were resolved from the reactant ion peak. Similarly to 2-butanol, mass spectrometry follow-on studies would have been required to confirm these assignments.

$n$-tetradecane vapour standards were also studied (see Table 4.5 for details) to establish the presence, or absence, of $n$-tetradecane product ions in the negative mode; the intent being to use it as a solvent carrier for 1-chlorohexane in subsequent studies. Although no product ions were observed in the mobility spectrum relating to $n$-tetradecane at IMS concentrations of between 8.2 µg m$^{-3}$ (1.1 ppb(v)) and 516.6 µg m$^{-3}$ (69.3 ppb(v)), its presence did lead to an increase in thermalised electrons, resulting in elevated abundances of $\{(\text{H}_2\text{O})_n\text{CO}_2\}$ and $\{(\text{H}_2\text{O})_n\text{O}_2\}$. The IMS responses observed with the introduction of the $n$-tetradecane permeation sources did follow this behaviour, by increasing reactant ion response in channels 9 and 10 (Figure 5.12). Increased quantity of reactant ions could be used in future work to extend the dynamic range from increasing the reactant ion reservoir.
Background corrected signal intensity against transverse IMS detector channel number data, obtained from permeation sources of \( n \)-tetradecane. The letters in the graph relate to the following dopant concentrations: A = 101.3 μg m\(^{-3}\), B = 181.5 μg m\(^{-3}\), C = 321.0 μg m\(^{-3}\), D = 368.9 μg m\(^{-3}\) and E = 516.6 μg m\(^{-3}\).

Figures 5.13 and 5.14 show the IMS product ion responses obtained from dispensing 2-butanol and 1-chlorohexane at steady-state concentrations for periods of 20 s, see Table 4.2. The product ion responses for 2-butanol (channels 3-5) indicated stable APCI formation (<5% RSD in signal intensity at all concentrations) across the concentration range 20.5 μg m\(^{-3}\) (6.8 ppb(v)) to 196.6 μg m\(^{-3}\) (65.3 ppb(v)). Similar product ion stability (<4.7% RSD in signal intensity) was observed for 1-chlorohexane dispensing over a concentration range of between 27.5 μg m\(^{-3}\) (5.6 ppb(v)) and 203.6 μg m\(^{-3}\) (41.5 ppb(v)).
Gas-phase dopant concentrations were calculated from the calibration obtained from the permeation sources (Section 4.2.5); based upon the summation of the total product ion responses. 3.1 ± 1.2 seconds were allowed for the system to stabilise after commencing PZX dispensing. This allowed adsorption of the dopant onto the internal surfaces to stabilise. Adsorption-based hysteresis was considered during the design of the interface unit and the materials used were selected to inhibit adsorption and suppress memory effects and carry over between operating states. Baseline signal intensities (i.e. original H$_2$O based reactant ion chemistries) were recovered within 3 seconds of stopping the PZX dispenser, indicating satisfactory clear-out of the dopant from the system. These results were encouraging for they demonstrated the capability of the PZX dispenser to control the APCI chemistry in the ion mobility reaction region over an order of magnitude of dopant concentrations dynamically and reversibly.
Figure 5.14 Transverse IMS signal intensity against scan time for the product ion responses obtained from dispensing steady-state concentrations of 1-chlorohexane into the transverse IMS. The black lines represent the responses from channel 11 in the negative mode; the grey lines, responses from the proposed chloride ions in channel 10. The data shown is background corrected, but an offset was introduced to the data in channel 11 to enhance the presentation clarity.

By applying a maximum split flow of 100 cm³ min⁻¹, a lowest 2-butanol concentration of 20.5 µg m⁻³ was produced, enabling a mean background-corrected signal intensity of 7.9 pA in channel 3. The dopant concentration could have been lowered by providing either another split flow at the interface, or through the introduction of a smaller-bore capillary tubing (e.g. 0.1 mm I.D.), causing increased resistance to mass flow. A more uncomplicated method of lowering the dopant gas phase concentrations would have been to increase the diluent gas flow rate at F₁, and this was considered during the experimental work flow. Experiments were devised to lower concentrations by increasing the F₁ flow to 400 cm³ min⁻¹. This was not successful as increasing the inlet flow rate beyond 150 cm³ min⁻¹ interfered with dispensing performance, reducing the stability of product ion formation. At an F₁ flow rate of 400 cm³ min⁻¹ product ion signals were completely suppressed for both dopants. The increased inlet gas flow around the PZX orifice was thought to have dried the nozzle, preventing the dispensing process. Higher dopant concentrations
than those detailed in Figures 5.13 and 5.14 were not attempted at this stage in the study, as the objectives were to prove the concepts of dopant APCI control and dynamic switching between water based (reactant ion) and dopant based (product ion) chemistries. Later studies using DMS were used to generate steady-state dopant responses at concentrations to beyond 950 cm$^3$ m$^{-3}$ (>300 ppb(v)) for 2-butanol (see Section 4.3).

The proposed 2-butanol monomer ion (channel 3 in the positive mode) increased linearly at IMS concentrations from 20.5 µg m$^{-3}$ (6.8 ppb(v)) to 127.5 µg m$^{-3}$ (42.4 ppb(v)), while the larger alcohol ion clusters represented in channels 4 and 5 increased linearly throughout the full concentration profile. The presence of the proposed high mobility chloride ion, ([(H$_2$O)$_n$Cl]$^-$, showed relatively high abundance at low 1-chlorohexane IMS concentrations between 27.5 µg m$^{-3}$ (5.6 ppb(v)) and 71.4 µg m$^{-3}$ (14.6 ppb(v)). This is seen in channel 10 in Figure 5.14. Increasing 1-chlorohexane concentrations beyond 106.8 µg m$^{-3}$ (21.8ppb(v)) saw the product ion signal shift to lower mobilities (channel 11). These data support the findings from the permeation source data obtained prior to dispensing the dopants (see Section 5.3).

5.4 The generation of transient dopant responses

Figure 5.15 shows the signal intensity vs time responses obtained from bolus dispensing of 2-butanol and 25% 1-chlorohexane in the n-tetradecane carrier under the conditions described in Section 4.2.3 and Table 4.1. The data were obtained by summing the background-corrected product ion responses from the dispensed dopants.

Linear regression relationships between dispensed mass (in ng) and mean integrated peak area (pA s$^{-1}$) were obtained for the summed product ions for both dopants, see Figure 5.16. The repeatability in peak area for each of the dispensed mass levels was between 1.28% RSD and 10.55%. No relationship between dispensed mass and RSD was discerned, indicating only random errors in the droplet dispensing process. The limit of detection for 2-butanol ($\mu + 3\sigma$) was 12.0 ng and 9.7 ng for 1-chlorohexane. These data show the response characteristics of the PZX dispenser operating digitally controlled ionisation processes. Once the gas-flows were set (see Section 4.2.3) the only other input required for generating these data was to apply the waveform command to the PZX dispenser through software control. In practice
this experimental procedure could be simplified further by writing command scripts to provide automated control of the dispensing process.

Figure 5.15  Product ion responses obtained from dispensing boluses of 2-butanol and 1-chlorohexane into the transverse IMS. The responses relate to the summation of the total product ion signals. 2-butanol responses are represented in blue, 1-chlorohexane signals in red.
Encouragingly, the response times for all these levels were in the order of 3 – 6 seconds (from baseline to baseline). These data indicated that the generation of dopant transients on time-scales compatible with analyte elution from a gas chromatograph was a possibility with the technique. Evidence of hysteresis was observed for the higher mass dispensing. A tailing factor, \( \rho \), of 1.5 seconds was calculated for 2-butanol dispensing of 496± 32 ng, where \( \rho \) was calculated from Equation 5.3

\[
\rho = \frac{a + b}{2a} \tag{Equation 5.3}
\]

where, \( a \) is the distance (s\(^{-1}\)) from the leading edge of the peak at 5% of the peak height to the point (s\(^{-1}\)) at peak height, and \( b \) is the distance (s\(^{-1}\)) from the point at peak height to the far edge of the peak (s\(^{-1}\)) at 5% of the peak height. These data contained few hysteresis phenomena and demonstrated how rapid and reversible control of APCI processes for both positive and negative mode dopants was possible. A graphical demonstration of this with DMS responses is shown in Figure 5.25. Additionally, calibration of transient dopant responses was also possible.

### 5.5 Steady-state control of common IMS dopants

Calibration data obtained from the permeation sources of acetone, dichloromethane and 4-heptanone are shown in Figures 5.17 to 5.19. The data were obtained from vial-based permeation vapour sources described in Section 4.2.5 and Tables 4.7 to 4.9. Acetone generated a product ion response in channel 3 in the positive mode. The relationship between acetone concentration (\( \mu \)g m\(^{-3}\)) and signal intensity (pA) in channel 3 was linear from 35.9 \( \mu \)g m\(^{-3}\) (14.8 ppb(v)) to 177.9 \( \mu \)g m\(^{-3}\) (75.4 ppb(v)). This response was attributed to the acetone monomer ion, \( \{(H_2O)C_3H_6O\}^+ \). At concentrations above 177.9 \( \mu \)g m\(^{-3}\) (75.4 ppb(v)) the response in channel 3 decreased, while the signal in channel 4 increased linearly throughout the full concentration profile studies, to 368.4 \( \mu \)g m\(^{-3}\) (156.1 ppb(v)). This lower mobility
response was attributed to be the acetone dimer ion, \( ((\text{H}_2\text{O})\text{2C}_3\text{H}_6\text{O})^+ \), obtaining the charge from the monomer ion as per Equation 2.16. A third product ion species for acetone was distinguished in channel 5 at IMS concentrations >73.4 µg m\(^{-3}\) (31.6 ppb(v)). The identities of these product ion responses were not clear, due to the lack of accompanying mass spectrometric data. Suffice to say some mass spectrometry would be helpful in precisely assigning these product ion species. The permeation rates from the acetone vapour sources (Table 4.7) prevented the production of IMS calibration standards below a concentration of 34.9 µg m\(^{-3}\).
Figure 5.17  Transverse IMS responses obtained from permeation sources of acetone. The top graph represents the background corrected signal intensity against the individual detector channels in the positive mode with changing dopant concentration. The letters relate to the following dopant concentrations: A = 34.9 μg m$^{-3}$, B = 73.4 μg m$^{-3}$, C = 144.2 μg m$^{-3}$, D = 212.8 μg m$^{-3}$, E = 297.6 μg m$^{-3}$ and F = 368.4 μg m$^{-3}$. The bottom graph shows the linear relationship of the signal intensity against dopant concentration, [D] / μg m$^{-3}$, from summing of the product ion responses in channels 3-5. The graph was used to calibrate the responses from dispensed acetone when developing a novel method for introducing acetone doping into IMS.
Permeation sources for 4-heptanone produced IMS responses of >22.5 pA in channels 3-6 in the positive mode. Responses in channels 4-6 were linear (R^2 between 0.988 and 0.993) over the full concentration range produced by the permeation vials, i.e. between 7.4 µg m^{-3} (1.6 ppb(v)) and 99.7 µg m^{-3} (21.6 ppb(v)). The response in channel 3 was linear from 7.4 µg m^{-3} to 42.3 µg m^{-3} (R^2 = 0.990). Beyond this concentration, there was a reduction in the relative increase in the response. This was attributed to the formation of proton-bound clusters (dimers) generating responses in the lower mobility channels. The ions in channel 3 were assigned to the 4-heptanone monomer ions. The relatively small range in concentration produced by these vials was the result of permeation rates of 9.62 – 89.83 ng min^{-1} from a compound which produces a vapour pressure of only 0.21 kPa at 20 °C. Follow-on studies would usefully use permeation sources with higher release rates.

Dichloromethane sources produced product ion responses in channels 11 and 12 in the negative mode. At analyte concentrations of between 26.6 µg m^{-3} (7.7 ppb(v)) and 59.8 µg m^{-3} (17.3 ppb(v)) an increase in the response in channel 10 was observed to -7.9 pA, followed by a subsequent decrease in this response with increasing concentration. The IMS response in channel 11 to the dichloromethane permeation standards was linear with increasing concentration over the full concentration range generated, from 26.6 µg m^{-3} (7.7 ppb(v)) to 386.9 µg m^{-3} (111.8 ppb(v)). This data appears similar to the product ion responses observed for 1-chlorohexane, and are indicative of the same dissociative electron capture processes. At lower halogen concentrations, it is proposed that chloride ions, \{(H_2O)_nCl\} were formed in the mobility cell, leading to the presence of high mobility signals associated with channel 10. Increasing concentrations of dichloromethane resulted in chloride addict formation, \{(H_2O)CH_2Cl_2\}^{-}, attributed to product ions detected in channels 11 and 12. Again, mass spectrometry would have been required to confirm this, although exact ion identification was not the purpose of this study.
Figure 5.18 Transverse IMS responses obtained from permeation sources of 4-heptanone. The top graph represents the background corrected signal intensity against the individual detector channels in the positive mode with changing dopant concentration. The letters relate to the following dopant concentrations: A = 7.4 μg m⁻³, B = 30.6 μg m⁻³, C = 51.9 μg m⁻³, D = 69.1 μg m⁻³ and E = 99.7 μg m⁻³. The bottom graph shows the linear relationship of the signal intensity against dopant concentration, [D] / μg m⁻³, for the summation of the product ion responses in channels 3-6. The graph was used to calibrate the responses from dispensed 4-heptanone.
Figure 5.19  Transverse IMS responses obtained from permeation sources of dichloromethane. The top graph represents the background corrected signal intensity against the individual detector channels in the positive mode with changing dopant concentration. The letters relate to the following dopant concentrations: A = 26.6 $\mu$g m$^{-3}$, B = 58.1 $\mu$g m$^{-3}$, C = 82.0 $\mu$g m$^{-3}$, D = 187.0 $\mu$g m$^{-3}$, E = 245.1 $\mu$g m$^{-3}$, F = 360.3 $\mu$g m$^{-3}$ and G = 386.9 $\mu$g m$^{-3}$. The bottom graph shows the linear relationship of the signal intensity against dopant concentration, [D] / $\mu$g m$^{-3}$, for the product ion response in channel 11. The graph was used to calibrate the responses from dispensed dichloromethane.

Figures 5.20 through 5.22 show the IMS responses obtained from dispensing acetone, 4-heptanone and dichloromethane at steady-state concentrations for
periods of 20 s (see Table 4.6 for the operational parameters used). The product ion responses for both positive-mode dopants were stable with 5% RSD for the signal intensity at all the concentrations studied. This was more stable than was expected, for acetone was observed previously to have relatively unstable dispensation characteristics (see Figure 5.6) observed during the PZX waveform optimisation experiments.

Dichloromethane responses in the negative mode were less stable than for the positive ion dopants. RSDs of between 8 – 18% in signal intensity were calculated for the steady-state concentrations relating to the dispensing of dichloromethane. This suggested a lack of stability in the dispensation process, a conclusion supported by droplet optimisation data (see Section 5.1).
Figure 5.20 Transverse IMS signal intensity against scan time for the product ion responses obtained from dispensing steady-state concentrations of acetone into the transverse IMS. The black lines represent the responses from channel 3, proposed to be from the acetone monomer ion. The grey lines represent responses from the proposed acetone dimer, generating responses in channel 4. The black dotted line expresses a third product ion species generating responses in channel 5. Concentrations at each level were calculated from permeation source data.

35.4 µg m⁻³
62.8 µg m⁻³
101.2 µg m⁻³
128.9 µg m⁻³
164.5 µg m⁻³
Figure 5.21  Transverse IMS signal intensity against scan time for the product ion responses obtained from dispensing steady-state concentrations of 4-heptanone into the transverse IMS. The black line represents the responses obtained from channel 3 in the positive mode. The most intense product ion for 4-heptanone was observed in channel 4 and represented in grey. The red data express the signals generated in channel 5, and a further product species shown by the black dotted line represents responses in channel 6.
Figure 5.22  Transverse IMS signal intensity against scan time for the product ion responses obtained from dispensing steady-state concentrations of dichloromethane into the transverse IMS. The principal product ion response, observed in channel 11 (negative mode) is expressed by the black line. The proposed chloride ion signals in channels 9 and 10 are represented in grey and the black dotted line, respectively.

It is important to note that all dopants required conditioning before the start of the experimental procedure to enable the correct degree of wetting at the PZX orifice head, so that dopant dispensing would proceed. This procedure involved using the purge gas supplying the dopant reservoir (see Section 3.3.3) to flush the syringe with the dopant for periods of 1-2 seconds at a purge pressure of 25 kPa. The waveforms were then initiated continuously at 1 kHz with the dispenser placed vertically over a clear sheet of paper to ensure the presence of dispensing prior to inserting the dispenser into the interface. For dopants with favourable dispensing properties (viscosities >1.00 Pa s⁻¹ at 20 °C) the operation was only required once, so 5-10 seconds conditioning time was sufficient. The operation was more challenging for the conditioning of acetone and dichloromethane, and required repeating five times for acetone to initiate dopant dispensing. This is an aspect of the system that requires further study and development.

<table>
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</tr>
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<td>270.2</td>
<td>27.6</td>
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5.6 Control of monomer and dimer chemistries in DMS

5.6.1 Studies with single dopants

Figure 5.23 shows background-subtracted DMS responses obtained from dispensing different mass fluxes, \( Q \), of 2-butanol into the DMS cell over the run time of the experimental campaign. The experimental conditions required to implement these mass fluxes are described in Section 4.3.2 and specifically given in Table 4.10 [197].

Two product ions were observed in the positive mode for 2-butanol dispensing, at compensation fields \( (E_c) \) of \(-166.6 \text{ V cm}^{-1}\) and \(-75.0 \text{ V cm}^{-1}\). The reactant ion peak appeared at \( E_c = -400.0 \text{ V cm}^{-1} \). A dispersion field 21 kV cm\(^{-1}\) was used for this study, yielding resolution of the product and reactant ions. At \( Q = 21 \text{ - } 132 \text{ ng min}^{-1} \), corresponding to a DMS concentration of \(17 \text{ - } 106 \mu g \text{ m}^{-3}\), only the response at \(-166.6 \text{ V cm}^{-1}\) was observed in the DMS spectrum. This is presented in the \( I \) (mV) vs \( E_c \) spectral plot in plot A, below Figure 5.23. A subsequent increase in the mass flux >132 ng min\(^{-1}\) produced the second product ion, at \( E_c = -75.0 \text{ V cm}^{-1} \). Plot B in Figure 5.23 spectrally demonstrates the simultaneous production of both product ions for 2-butanol at \( Q = 244 \text{ ng min}^{-1} \). The intensity of the first product ion decreased upon continued increases of \( Q \) to baseline levels at mass fluxes >704 ng min\(^{-1}\) (2-butanol concentration >563.2 \mu g \text{ m}^{-3}\). Plot C in Figure 5.23 shows a DMS spectrum displaying absence of the primary product ion, commensurate with an increase in the second product ion intensity. This behaviour is characteristic of monomer/dimer product ion formation of alcohols [12,124,198] in APCI systems in the positive ionisation mode following the equilibration scheme (Equation 5.4).
At mass fluxes < 704 ng min\(^{-1}\), a protonated monomer ion, expressed as the intermediate in Equation 5.4, was generated, and the product ion observed at a compensation field of -166.6 V cm\(^{-1}\) may be assigned to this entity. Increasing the concentration in the reaction region resulted in the formation of a proton-bound dimer cluster ion, observed at -75 V cm\(^{-1}\). Dimer ion clusters were formed at higher analyte concentrations due to the greater potential for collisions of the ion swarms. Similarly to the data generated from the transverse IMS instrument, mass spectrometers would need interfacing to the mobility cell for confirmatory analysis of ion clusters. The relationship between these entities and the mass flux of 2-butanol in the reaction region is summarised in Figure 5.24, which shows the effect on the observed mean ion intensities (mV) on changing 2-butanol concentration. The mean RIP intensity in the positive mode for 2-butanol dispensing was shown to decrease linearly with increasing mass flux (\(R^2 = 0.984\)). There was also a linear increase in the mean intensity of the proposed 2-butanol dimer (\(R^2 = 0.975\)) at mass fluxes between 132 ng min\(^{-1}\) and 1230 ng min\(^{-1}\).
Figure 5.23 Background-corrected DMS responses for 2-butanol dispensing at varying mass fluxes, from 21 – 1230 ng min⁻¹. The top graph represents response intensity (mV) vs scan time. Graphs A, B and C show the depicted response intensities vs applied compensation field, $E_c$, at various points along the main graph, as shown. Graph A demonstrates the production of just the proposed alcohol monomer ion species, graph B presents the production of both the monomer and dimer ion swarms, and graph C, only the alcohol dimer ion.
Figure 5.24  Mean ion response intensity vs 2-butanol mass flux for the dispensing of 2-butanol into the DMS cell. The proposed ion formation is given. All data were subjected to initial background-correction. The ionisation processes follow those modelled in Figure 2.9.

Figure 5.25 demonstrates the ability of the novel system to control the ion production stability and dynamics arising from dispensing 2-butanol into the DMS cell. Control of ionisation chemistry was a primary objective in these investigations. The precision of the observed responses was in the range 2.2% - 7.9% RSD at all mass flux levels in the test sequence. The switching speed between concentrations, described in terms of stabilisation time, was 3.1 ± 1.2 secs from the point of changing the split flow at $F_3$.

The transit time though the dispenser was approximately 800 ms and the lag is thought to be attributable to adsorption phenomenon onto the internal surfaces of the gas-lines and jet-pump [197]. However, no hysteresis or memory artefacts were observed with the use of a jet-pump, and the adsorption phenomenon was reversible.

To demonstrate the behaviour of switching speed and stabilisation in the system, Figure 5.25 also shows two close up data shots; one for the increase in 2-butanol mass flux from 244 – 514 ng min$^{-1}$, and the other representing a decrease in mass flux from 1230 – 969 ng min$^{-1}$. The data generated from the PZX dispensing of 2-butanol demonstrate the suitability of the PZX dispensing technology for providing flexible control of dopant ionisation processes in both IMS and DMS systems. The system can be programmed, for example, to provide a dopant concentration which
permits only the production of monomer dopant chemistry, allowing for potentially more selective and optimisable analysis of samples.
Figure 5.25 Plot of background-corrected signal intensity vs scan time for 2-butanol dispensing into the DMS cell. The letters represent the following mass fluxes, in ng min⁻¹: A = 0, B = 21, C = 132, D = 244, E = 514, F = 704, G = 969 and H = 1230. Control of the alcohol monomer, dimer and RIP is demonstrated. The captions above the main figure are close-ups demonstrating the switching of dopant mass flux, from 514 – 704 ng min⁻¹ (top left graph), and from 1230 – 969 ng min⁻¹ (top right graph). The dashed lines represent the physical point where the mass flux was altered.
Only one product ion, present at a compensation field of -356.2 V cm\(^{-1}\), was observed from the dispensing of 1-bromohexane in the negative ion mode. The background-corrected responses for 1-bromohexane dispensing vs scan time are shown in Figure 5.26. The RIP was present at \(E_c = -402.0\) V cm\(^{-1}\), from the applied RF field of 21 kV cm\(^{-1}\). The ion intensity concentration relationship is indicative of the presence of two dissociative ionisation processes, both of which generated a bromide ion cluster, \((\text{O}_2)_n\text{C}_6\text{H}_{13}\text{Br})_n\). At mass fluxes <1918 ng min\(^{-1}\), the production of the bromide ion cluster was inversely proportional to the loss of charge from the reactant ion, suggesting collisional-based charge transfer followed by dissociation. Above 1918 ng min\(^{-1}\) the yield of bromide ion clusters was greater than the loss of negative reactant ion species, consistent with direct ionisation of the 1-bromohexane. Such ionisation processes have been previously demonstrated using mass spectrometry in the literature [12,199]. No RIP signal was observed at and beyond \(Q = 1918\) ng min\(^{-1}\), which corresponded to 1-bromohexane concentration of 1534 µg m\(^{-3}\). The increase in product ion response above this level could only be attributable to direct ionisation of the dopant molecules. The mean background-corrected response intensity, \(I\), vs \(Q\) relationship is plotted in Figure 5.27. This highlights the discontinuities in product ion formation between dissociative electron capture processes from the RIP at dopant mass fluxes <1918 ng min\(^{-1}\), and direct 1-bromohexane ionisation. The linear regression \(R^2\) value for the mean increase in signal intensity vs \(Q\) for the 1-bromohexane cluster was 0.973 at mass fluxes between 149 ng min\(^{-1}\) and 1918 ng min\(^{-1}\).

Note that in the positive mode, the RIP intensity (380 mV at \(Q = 0\) for 2-butanol) is not replenished by the product ions for the dopant. Once the RIP signal has been depleted to 17 mV, the mean 2-butanol dimer signal intensity is 197 mV. The reasons for this are unclear, but are thought to due to the formation of other ion clusters that are not stable and/or not resolved within the DMS cell.
Figure 5.26 Background-corrected DMS responses for 1-bromohexane dispensing at varying mass fluxes, from 149 – 2644 ng min⁻¹. The top graph represents response intensity (mV) vs scan time. Graphs A and B show the response intensities vs applied compensation field, $E_c$, at various points along the main graph, as shown. Graph A demonstrates the production of the bromide ion cluster, at a mass flux of 904 ng min⁻¹. Graph B shows a DMS spectrum taken at a 1-bromohexane mass flux of 2644 ng min⁻¹. The RIP is no longer observed.
Figure 5.27 Mean ion signal intensity vs mass flux for 1-bromohexane dispensing into the DMS cell. A represents the region where bromide cluster ions were formed from dissociative electron capture processes from the RIP, and B represents the region concerning direct ionisation of the dopant, at mass fluxes >1918 ng min⁻¹. The RIP in this region is saturated, displayed by the spectrum in Figure 5.26 B.

The stability of product ion control arising from dispensing of 1-bromohexane is demonstrated in Figure 5.28, presented as a plot of intensity (mV) vs scan time of the experimental test sequence. As for 2-butanol dispensing, the variance in bromide cluster ion intensity was calculated to be between 1.2% and 7.9% at all concentrations provided by the PZX dispenser and interface manifold. Stabilisation time for the product ion swarm, calculated as the time taken to reach <3 standard deviations of the mean intensity at a given level, was 2.2 ± 1.5 sec, demonstrating further the level of potential dopant control afforded by the novel instrumentation. Close-ups highlighting this are shown above the main graph in Figure 5.28. The jet pump (see Section 3.5) appeared to provide efficient transfer of dopant vapour to the DMS cell. These stability data are similar to those obtained from the transverse IMS experiments.
Figure 5.28  Plot of background-corrected signal intensity vs scan time for 1-bromohexane dispensing into the DMS cell. The letters represent the following mass fluxes, in ng min⁻¹: A = 0, B = 149, C = 512, D = 904, E = 1229, F = 1602, G = 1918 and H = 2644. The captions above the main figure are close-ups demonstrating the switching of dopant mass flux, from 149 - 512 ng min⁻¹ (top left graph), and from 1229 – 904 ng min⁻¹ (top right graph). The dashed lines represent the physical point where the mass flux was altered. The x-axis range for the top graphs was 10 seconds in both cases.
5.6.2 Studies with mixed dopants

A specific objective of these studies was to prove the concept of simultaneous control of positive and negative mode doping through PZX dispensers (see Section 1.5). Figures 5.29 and 5.30 show the background-corrected ion signal intensity vs scan time relationships obtained from dispensing the 50% 2-butanol, 1-bromohexane mixture at different mass fluxes across the experimental sequence. The proposed monomer and dimer responses for 2-butanol were observed at the same compensation fields as for individual dispensing ($E_c = -166.6$ and $-75.0 \text{ V cm}^{-1}$ respectively). The bromide cluster, observed from individualised dispensing of 1-bromohexane again produced a response at $E_c = -356.2 \text{ V cm}^{-1}$ in the negative mode, from the applied RF field of 21 kV cm$^{-1}$. The reactant ion peaks in both modes were also consistent in intensity and position to those observed in the individual dopant studies.
Figure 5.29 Background-corrected positive mode DMS responses obtained from dispensing the 2-butanol, 1-bromohexane mixture. The top graph represents response intensity (mV) vs scan time. Graphs A, B and C show individual DMS spectra at specific points along the main graph, as shown. Graph A demonstrates the production of just the proposed alcohol monomer ion species for 2-butanol, graph B presents the production of both the monomer and dimer ion swarms, and graph C, only the alcohol dimer ion.
Figure 5.30  Background-corrected negative mode DMS responses obtained from dispensing the 2-butanol, 1-bromohexane mixture. The top graph represents response intensity (mV) vs scan time during the experimental sequence. Graphs A and B show individual DMS spectra at specific points along the main graph, as shown. Graph A demonstrates the production of the bromide ion cluster, spectrally resolved from the RIP. Graph B shows saturation of the bromide product ion swarm, generated at a mass flux of 1325 ng min\(^{-1}\).
No alternative ion clusters were observed in either ionisation modes, suggesting that the same APCI processes were present as for individual dopant dispensing. To test this hypothesis, the mean product ion signal intensities at different mass flux levels from the individual and mixed dopant experiments were compared using t-test data. Regression graphs, showing product ion intensity (mV) vs $Q$ were constructed for the 2-butanol dimer and 1-bromohexane product ions to estimate the responses from the mixed dopant sample that would be achieved from the specific mass fluxes used in the single dopant experiments. The regression graphs are shown in Figure 5.31 and the t-statistic data pertaining to these are presented in Tables 5.12 and 5.13. The null hypothesis, $H_0 = $ no significant difference in ion intensity between the individual and mixed dopant actuations, was retained (to $P = 0.05$) at every mass flux for 2-butanol, indicating that the ionisation chemistries were equivalent in the individually and mixed dispensed dopants. The same hypothesis was retained for the 1-bromohexane data. These data demonstrate the suitability of the novel instrumentation for providing simultaneous control of ionisation chemistries of mixed dopants in both positive and negative ionisation modes.
Figure 5.31  Mean signal intensity vs mass flux data obtained for individual and mixed dispensed dopants. The top graph shows the mean background subtracted responses for the 2-butanol dimer ion. The dimer intensities pertaining to the individually dispensed 2-butanol are represented in circles, and the mixed dispensing data with diamonds. The bottom graph shows the mean background subtracted bromide product ion intensity data, where the individually dispensed 1-bromohexane is represented in circles and the mixed dopant data in diamonds. These data were used to calculate the t-statistics, displayed in Tables 5.12 and 5.13.
Table 5.12  t-statistic data for the comparison of the dimer ion signal intensity for 2-butanol between the individual and mixed dispensed dopant modes. $\bar{x}_1$ represents the mean signal intensity for the individually dispensed 2-butanol. Critical t-value to $P = 0.05 = 1.96$.

<table>
<thead>
<tr>
<th>$Q$ / ng min$^{-1}$</th>
<th>$\bar{x}_1$ / mV</th>
<th>$\bar{x}_2$ / mV</th>
<th>$s_1$</th>
<th>$s_2$</th>
<th>t-stat</th>
<th>$H_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>5.48</td>
<td>3.65</td>
<td>17.53</td>
<td>17.95</td>
<td>0.074</td>
<td>retained</td>
</tr>
<tr>
<td>132</td>
<td>16.83</td>
<td>22.18</td>
<td>75.74</td>
<td>50.66</td>
<td>-0.050</td>
<td>retained</td>
</tr>
<tr>
<td>244</td>
<td>49.83</td>
<td>40.89</td>
<td>194.35</td>
<td>361.78</td>
<td>0.032</td>
<td>retained</td>
</tr>
<tr>
<td>514</td>
<td>92.47</td>
<td>85.98</td>
<td>656.50</td>
<td>569.09</td>
<td>0.007</td>
<td>retained</td>
</tr>
<tr>
<td>704</td>
<td>122.15</td>
<td>117.71</td>
<td>781.76</td>
<td>685.02</td>
<td>0.004</td>
<td>retained</td>
</tr>
<tr>
<td>969</td>
<td>140.31</td>
<td>161.96</td>
<td>561.24</td>
<td>574.88</td>
<td>-0.027</td>
<td>retained</td>
</tr>
<tr>
<td>1230</td>
<td>187.05</td>
<td>205.55</td>
<td>879.12</td>
<td>945.02</td>
<td>-0.015</td>
<td>retained</td>
</tr>
</tbody>
</table>

Table 5.13  t-statistic data for the comparison of the product ion signal intensity for 1-bromohexane between the individual and mixed dispensed dopant modes. $\bar{x}_1$ represents the mean signal intensity for the individually dispensed 1-bromohexane. Critical t-value to $P=0.05 = 1.96$.

<table>
<thead>
<tr>
<th>$Q$ / ng min$^{-1}$</th>
<th>$\bar{x}_1$ / mV</th>
<th>$\bar{x}_2$ / mV</th>
<th>$s_1$</th>
<th>$s_2$</th>
<th>t-stat</th>
<th>$H_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>149</td>
<td>35.55</td>
<td>24.37</td>
<td>199.79</td>
<td>73.31</td>
<td>0.040</td>
<td>Retained</td>
</tr>
<tr>
<td>512</td>
<td>57.64</td>
<td>53.82</td>
<td>259.38</td>
<td>168.34</td>
<td>0.011</td>
<td>Retained</td>
</tr>
<tr>
<td>904</td>
<td>82.69</td>
<td>85.62</td>
<td>595.33</td>
<td>194.98</td>
<td>-0.004</td>
<td>Retained</td>
</tr>
<tr>
<td>1229</td>
<td>100.86</td>
<td>111.99</td>
<td>514.36</td>
<td>441.30</td>
<td>-0.015</td>
<td>Retained</td>
</tr>
<tr>
<td>1602</td>
<td>129.55</td>
<td>142.25</td>
<td>505.24</td>
<td>281.42</td>
<td>-0.018</td>
<td>Retained</td>
</tr>
<tr>
<td>1918</td>
<td>150.46</td>
<td>167.89</td>
<td>737.25</td>
<td>435.59</td>
<td>-0.017</td>
<td>Retained</td>
</tr>
<tr>
<td>1230</td>
<td>173.47</td>
<td>226.78</td>
<td>988.78</td>
<td>585.21</td>
<td>-0.039</td>
<td>Retained</td>
</tr>
</tbody>
</table>

Equations 5.5 – 5.8 describe the linear regressions that were calculated for the RIP and product ions for both dopants. There was no evidence that indicated the mixed dopants interfered with the generation of ions in the opposite polarity mode; essentially this indicates that the positive and negative ionisation processes were independent of one-another [197].
5.7 Analysis of 2-octanol using 2-butanol as a dopant

Figure 5.32 shows the DMS spectral profile that was generated from 52.8 µg m\(^{-3}\) 2-octanol, at an RF field of 23.6 kV cm\(^{-1}\) introduced as a mixture of R-(-) and S-(+) enantiomers from permeation sources. The RF field was chosen for the purpose of maximizing the analytical space for resolving potential ion clusters upon dopant introduction. 2-octanol provided two stable ion clusters, at compensation fields \((E_c)\) of -146.6 and 26.6 V cm\(^{-1}\). A screenshot of the contour plot generated from the permeation sources is displayed in the top graph of Figure 5.32; a signal-averaged spectrum for the sources is displayed in the bottom graph.
Figure 5.32  DMS responses obtained from 58.2 μg m⁻³ 2-octanol, introduced into the spectrometer using pre-calibrated permeation sources. The above graph is a screenshot taken from the Sionex Expert™ software, demonstrating the position of product ions; a signal-averaged spectrum of intensity vs compensation field is shown in the below graph.
It was proposed from concentration-based principles [12,123,200] (see Section 2.5.2, and 5.6.1 for comparison with 2-butanol work) that the product ion swarm observed at -146.6 V cm\(^{-1}\) was assigned as the 2-octanol monomer ion, \(\{(\text{H}_2\text{O})\text{C}_8\text{H}_{17}\text{OH}\}\)\(^+\), and the species at 26.6 V cm\(^{-1}\), the 2-octanol dimer, \(\{(\text{H}_2\text{O})2\text{C}_8\text{H}_{17}\text{OH}\}\)\(^+\). There was no evidence of enantiomeric separation of the two forms of 2-octanol at this stage.

The introduction of R-(\(-\))-2-butanol through the PZX-DMS interface generated the responses described in Figure 5.33. (R)-(\(-\))-2-butanol was dispensed as the dopant species at DMS concentrations from 60.2 µg m\(^{-3}\) to 945.0 µg m\(^{-3}\), using the procedure described in Section 4.4. The experimental objective was to obtain enantiomeric separation of 2-octanol. The graph in Figure 5.33 displays the screenshot of the DMS responses obtained from this experiment. The product ion responses could be described in four clear response regions, displaying distinct and defined product ion behaviour. In region 1, expressed by number 1 in the screenshot, only the 2-octanol product ions were present in the DMS spectra. At this stage, there was no PZX dispensing of the (R)-(\(-\))-2-butanol dopant into the system. A signal averaged DMS spectrum, employing background correction (see Section 4.4) of region 1 is shown as graph 1 in Figure 5.34.

Different ion clusters were observed when the system was doped for 30 s at 60.2 µg m\(^{-3}\)(R)-(\(-\))-2-butanol. The 2-octanol product ion intensities were reduced to background, and two alternative ion species were present at compensation fields of -26.6 V cm\(^{-1}\) and -186.6 V cm\(^{-1}\). This region is highlighted as number 2 in the contour plot in Figure 5.33. A background-subtracted, signal averaged spectrum, representing ion signals at region 2 is shown in graph 2 in Figure 5.34. The ion swarm at -186.6 V cm\(^{-1}\) was attributed to the (R)-(\(-\))-2-butanol monomer ion. This was determined in the absence of the 2-octanol permeation standards, achieved by closing the needle valve controlling the vapour flow rate exiting the test atmosphere generator (TAG) (Figure 4.8). The ion species present at \(E_c = -26.6 \text{ V cm}^{-1}\) was undeterminable, due to the lack of accompanying mass spectrometry data, but could have been a cluster ion swarm involving the (R)-(\(-\))-2-butanol and 2-octanol moieties. If so, (R)-(\(-\))-2-butanol effectively acted as a dopant for the 2-octanol. Interestingly, the signal intensity of the undetermined product ion was 3.5 times higher than the corresponding 2-octanol dimer ion swarm in region 1 (i.e. 28 mV to 8 mV respectively).
Doping the system with 945.0 µg m⁻³ (R)-(-)-2-butanol produced DMS responses corresponding to region 3 in Figure 5.33. Again, a signal-averaged spectrum demonstrating the ion behaviour at region 3 is presented in graph 3, Figure 5.34. A gradual shift in the product ion chemistry was observed from a compensation field of -26.6 V cm⁻¹ to -53.4 V cm⁻¹, corresponding with a decrease in intensity for the 2-butanol monomer ion, described in region 2. At region 4 in the experimental programme, where the system was doped with 945.0 µg m⁻³, the product ion at -53.4 V cm⁻¹ increased to a background-corrected intensity of 74.5 mV. This ion species was attributed to the (R)-(-)-2-butanol dimer ion swarm. This was confirmed through dispensing a blank sample of (R)-(-)-2-butanol at a steady-state concentration of 195 µg m⁻³ for 30 s in the absence of 2-octanol; obtained by shutting off the needle valve emanating from the TAG (Figure 5.35). The RIP was found to deplete to baseline values at dopant concentrations of 945.0 µg m⁻³.

The 3.5-fold increase in the signal intensity of the adduct in region 2 demonstrates the potential of doping to increase the sensitivity of the analytical response, and modify its differential mobility, by altering the APCI processes in the DMS cell. The data in this study provided no evidence of chiral resolution of the 2-octanol enantiomers. More extensive studies would have been required to determine whether enantiomeric separation is possible using the novel technology. Unfortunately, time constraints only permitted this basic investigation, and the experiment was only attempted once.
Figure 5.33  Raw DMS screenshot obtained from dispensing 60.2 - 945.0 μg m$^{-3}$ (R)-(-)-2-butanol as a dopant to the DMS cell in the presence of 2-octanol, introduced to the DMS cell at 52.8 μg m$^{-3}$ via permeation sources. 1 represents the product ion responses in the absence of the dopant. 2 represents the responses from dispensing at 60.2 μg m$^{-3}$. 3 represents the increase in the concentration of the dopant to 945.0 μg m$^{-3}$. 4 represents the responses generated from 945.0 μg m$^{-3}$ (R)-(-)-2-butanol.
Figure 5.34  Signal averaged DMS spectra obtained from dispensing (R)-(-)-2-butanol into the DMS cell in the presence of 52.8 µg m$^{-3}$ 2-octanol.

The graph numbers represent the following (R)-(-)-2-butanol concentrations, in µg m$^{-3}$: 1 = 0, 2 = 60.2, 3 = 60.2 – 945.0, 4 = 945.0.
Figure 5.35 Mean background-corrected signal intensity vs compensation field obtained from dispensing (R)-(−)-2-butanol at a steady-state concentration of 195 µg m$^{-3}$ into the DMS cell. This was a blank sample obtained in the absence of 2-octanol, and was used to determine the positions of the 2-butanol monomer and dimer ions at an RF field of 23.6 kV cm$^{-1}$. The instrumental conditions required to achieve a (R)-(−)-2-butanol concentration of 195 µg m$^{-3}$ are described in Table 4.10.
Chapter 6

Conclusions and Future Work

6.1 Overview

Existing dopant introduction systems in ion mobility and differential mobility spectrometers do not comprise the technology required to permit the dynamic control of APCI dopant chemistries in the ion mobility cell. Systems exist where only one type of dopant can be introduced at a single concentration [13,163,201].

Instruments that can utilise multiple dopant chemistries are limited in their applicability to permit simultaneous introduction of specified dopant ranges. These limitations restrict the ability of mobility spectrometers to optimise the detection sensitivity and specificity for ranges of target analytes. This is especially relevant in the analysis of complex samples (e.g. fuels, biological fluids) where multiple dopants at specific concentrations may be required for enabling the optimised detection of a multiple analyte sequence. Mobility spectrometers hyphenated to gas chromatographs as a pre-separation step may also require dopant influxes to permit specific analyte detection on a time-scale compatible with elution of that analyte. The objectives for this study were to devise, implement, and characterise a novel technology for IMS that would overcome these existing limitations, by providing ACPI control of multiple dopant chemistries at a range of concentrations above two orders of magnitude. The objectives included in particular enabling the technology to be compatible with both ion mobility and differential mobility spectrometers.

PZX dispensers were shown in previous work to be suitable devices for controlling and calibrating analytical responses when used as sample introduction methods in GC [16]. Recent studies have also demonstrated the potential of vapour generation utilising PZX technology for calibrating IMS responses of explosives [113]. Work for the current study took the hypothesis that the control and calibration of dopant vapours in IMS and DMS could be achieved by interfacing PZX dispensers to mobility
spectrometers through the facilitation of an interface, comprising gas management and heating systems.

**6.2 Droplet optimisation studies and preliminary work**

The central composite design (CCD) approach for optimising droplet production in both the commercially available and purpose built PZX systems enabled optimal bipolar waveform methods to be generated in around 15 minutes for the selected dopants, 2-butanol, 1-chlorohexane, acetone, 4-heptanone, dichloromethane and 1-bromohexane. 70.1% - 96.1% precision in droplet volume, $P \gamma_d/\%$, was achieved under the optimised waveforms, generating individual droplet masses of between 40 ng and 73 ng (see Section 5.1). There was less stability in dispensing liquids with viscosities $<0.01 \text{ g / m s}^{-1}$ at 20 °C, where $P \gamma_d/\%$ was 70.1 – 90.2% (Figure 5.6).

The relationship between droplet precision and viscosity was demonstrated in Figure 5.6, where negative correlations were observed. Importantly for these studies, sufficient data correlations in terms of mean dispensed droplet volume, $\gamma_d$, were determined for both the commercial and purpose built systems (Figure 5.7). The correlations proved that the data was transferrable between systems, and highlighted the importance of using the commercially based equipment prior to designing the purpose built device. Additionally, the extra features available in the commercial unit (i.e. temperature and pressure control) enabled the modelling of these physical parameters on droplet volumes. The knowledge developed from these data allowed temperature and pressure boundaries to be defined for the purpose built system, and to ensure future quality control.

Alternatively, the optimisation work could have been expanded to incorporate back-pressure levels as a continuous variable to the CCD model, which may have further improved the dispensing performance. These experimental measures were not undertaken due to the significantly increased experimental steps that would have been required (27 factorial levels in the CCD for five factors as opposed to 17 for four) and the extra design difficulty that would have resulted from accurately lowering and controlling the reservoir temperature in an uncontrolled laboratory environment.

In addition to optimising the waveforms to generate controlled droplet production, the CCD model also enabled an understanding of the relative impact of the factor variables on droplet precision. The dwell time, $t_d$, and dwell voltage, $V_d$, of the
bipolar wave were the factors that produced the greatest impact on the droplet precision for every dopant in the studies, producing absolute coefficients in response of between 15 to 26 times that of the echo time, $t_e$, and echo voltage, $V_e$ (Figure 5.2).

Reservoir temperature, $T_r$/°C and waveform frequency, $\omega$/Hz, were shown in gravimetric studies to effect values for $\gamma_d$ when dispensing liquids under the optimized waveform settings. Increasing $T_r$/°C to 30 °C caused an increase in $\gamma_d$ to between 200% and 300% of the original mean droplet volumes at 22 °C. This was due to decreased fluid viscosity at higher reservoir temperatures. Increased values of $\omega$/Hz to 2000 Hz produced mean droplet volumes between 47.3% and 57.4% of the original droplet sizes calculated when dispensing at 500 Hz and 1000 Hz. The reasons for this were the destructive interferences of consecutive waves at higher frequencies, defined in previous work [188].

The droplet volume and precision data gained from these optimisation studies demonstrated the possibilities for controlled dispensing of candidate dopants, exhibiting a range of physical and ionisation properties. The data were cross-validated between two systems using both graphical (droplet imaging) and gravimetric methods to ensure data repeatability, and accuracy. These data would be required in future studies for the purpose of ensuring the accuracy for quantifying dopant concentration in the PZX-IMS interface.

6.3 Design and construction of the PZX-IMS/DMS interface

Dopant dispensing optimisation studies on the commercial JetLab4 instrumentation provided valuable knowledge of the environmental and design parameters that would be required for interfacing of the PZX dispensers to IMS transport gas inlets. Temperature studies (see Section 5.1.2) demonstrated the importance of thermal insulation of the dispenser to temperatures below 30 °C. The following design criteria were defined from the experience gained with these preliminary studies:

- Control of PZX orifice temperature to below 30 °C. This necessitated the use of thermal insulating material from the heating block required for droplet vaporization. PTFE was chosen due to its low thermal conductance.
- Back-pressure of -0.86 ± 0.52 kPa required to be supplied to the liquid reservoir, for preventing spontaneous dispensing of candidate dopants.
- Gas management manifold enabling a positive ("purge") pressure of 20.00 ± 5.00 kPa to be applied on demand to the reservoir, for the purpose of flushing a contaminated/blocked PZX orifice.
- Efficient transport of dispensed liquid through the interface, enabled through turbulent mixing of droplets with carrier gas stream of filtered air. The design of the interface body would also facilitate air turbulence, through cylindrical orifice features (Figure 3.14).
- Efficient volatilisation of dispensed liquid in the interface, enabled through an aluminium heating body.

The purpose built dispenser and interface were validated according to droplet volume data from the preliminary optimisation studies. t-test data (Table 5.9) confirmed that the purpose built instrumentation gave statistically the same droplet volumes as the JetLab4 device. This was an important find, which proved the transferability of waveform methods between different systems. No studies were undertaken to confirm inter-laboratory reproducibility statistics, due mainly to cost. The PZX-IMS interface was also validated for its gas flow regulation and control using regression statistics, temperature profiles at given heating block temperatures and contamination studies (Section 3.3.6). These studies were an essential part of determining the suitability and accuracy of the designed instrumentation for enabling dopant vapour control in the mobility spectrometers.

### 6.4 Calibration and control of dopant chemistry in transverse IMS

The purpose built PZX dispenser for this study enabled continuous and transient IMS responses to be generated for 2-butanol, 1-chlorohexane, acetone, 4-heptanone and dichloromethane dopants. The dopant concentrations were controlled dynamically by manipulating needle valve controls at a designed interface between the dispenser and the IMS cell. The interface comprised a controlled influx of filtered compressed air of flow rates between 100 cm³ min⁻¹ and 250 cm³ min⁻¹, for the function of transporting the dispensed liquids through the interface manifold, and an aluminium
heating block to vaporise the dispensed dopants. Details of the interface design are
given in Section 3.3.5.2.

Control of the signal intensities relating to dopant product ions to within 5% RSD for
2-butanol were calculated at dopant concentrations between 20.5 µg m$^{-3}$ (6.8 ppb(v))
and 196.6 µg m$^{-3}$ (65.3 ppb(v)). Similar control (>4.7% RSD) in signal intensities
relating to 1-chlorohexane, acetone and 4-heptanone were calculated at
concentrations between 27.5 µg m$^{-3}$ and 203.6 µg m$^{-3}$. There was lesser control of the
product ion responses for methylene chloride, with between 8-18% RSD in signal
intensity for the individual channel responses at concentrations between 27.6 µg m$^{-3}$
(8.0 ppb(v)) and 270.2 µg m$^{-3}$ (78.1 ppb(v)). This was the result of the relatively poor
precision in droplet volume for methylene chloride, observed in the optimisation
studies. This indicated a potential limitation of the technology for the reproducible
dispensing of liquids with relatively low viscosities (nominally below 0.01 g / m s$^{-1}$),
although a suitable carrier, such as n-tetradecane could be used in future work, as
proven with the dispensing of 1-chlorohexane (see Section 5.1.2). The actual
identities of the product ions produced in these studies were proposed based on
contemporary IMS ionisation theory, but could not be determined experimentally due
to lack of accompanying mass spectrometry data. It is the intention of future studies
to interface mass spectrometry for confirmatory diagnosis of APCI processes.

The dopant control data for the transverse IMS studies substantiate the hypothesis
that the novel PZX-IMS technology could be used to control the APCI chemistry of
dopants in both the positive and negative ionisation modes. The device importantly
enabled rapid switching, in the order of 3.1 ± 1.2 seconds (Section 5.6.1), between a
doped and an undoped system. The silica-based materials throughout the interface
unit and heating at the interface facilitated the reduction in hysteresis effects,
allowing for rapid ionisation control.

The device suffered from limitations in its ability to dilute further the dopant vapours
by introducing an inlet flow rate > 250 cm$^3$ min$^{-1}$. It was determined experimentally
that the influx of turbulent air flow above 250 cm$^3$ min$^{-1}$ disrupted the dispensing
process by reducing the degree of wetting at the orifice tip, preventing higher diluent
flow rates with the current interface design. A further limitation of the work was the
time taken to manually control the degree of wetting at the PZX orifice required to
dispense the dopants under their optimised waveforms. Although this process was
facilitated by incorporating a purge pressure valve into the pneumatic system of the
dispenser (see Section 3.3.3), an automated method would be constructive in future studies.

The dopant studies in transverse IMS also proved the concept of enabling transient dopant signals to be generated by dispensing a pre-determined fixed number of droplets through the interface. This process was achieved using 2-butanol and 25% 1-chlorohexane in \( n \)-tetradecane. Linear relationships \((R^2>0.99)\) between dispensed mass of dopant (in ng) and integrated peak area \((pA \text{ s}^{-1})\) were obtained for both dopants, for dispensed masses of between 62 ± 4 ng and 496 ± 32 ng for 2-butanol, and between 24 ± 2 ng and 384 ± 20 ng for 1-chlorohexane (see Section 5.4). These data proved that dopant calibration in IMS using PZX dispensing was a potentiality using the novel technology. Importantly for this work, the peaks relating to bolus dispensations were of the order of 4-6 seconds, confirming the hypothesis that dopants could be introduced by the technology on a time-scale compatible with analyte elution from a gas chromatograph. This principle was a defined objective of this thesis, and could open future possibilities for introducing multiple dopant moieties as transients at pre-defined points in a chromatographic run.

6.5 Control of monomer and dimer chemistry in DMS

The hypothesis of controlling monomer/dimer relationships of dopants in DMS was proven in this part of the study, by dispensing 2-butanol at steady-state mass fluxes of 21–1230 ng min\(^{-1}\) into a stand-alone differential mobility spectrometer. Only the proposed monomer was observed for 2-butanol at stable DMS mass fluxes of 21 – 132 ng min\(^{-1}\), whereas a second product ion, the alcohol dimer, was determined at mass fluxes above 132 ng min\(^{-1}\). This data, represented in Figures 5.23 – 5.25, demonstrated the potential of the system to deliver either the monomer ion, the dimer ion, or a combination of the two. These findings may benefit future studies through tailoring of the desired dopant chemistry to the ion mobility cell, thereby controlling the types and concentrations of ion clustering between the analyte and dopant.

This work also demonstrated the potential for interfacing the PZX technology to a differential mobility spectrometer for the first time. A jet pump was required to transport the dispensed dopants through the interface and into the DMS cell due to pressures of around 108 kPa present in the DMS transport gas (see Figure 3.19). Dopant responses were stabilised at 3.1 ± 1.2 seconds from the point of
manually changing the dopant concentration through manipulation of the interface split, suggesting that the jet pump did not contribute to hysteresis effects. Similarly to the results obtained from the transverse IMS, reactant ion responses were reached within 3 seconds from ceasing dopant dispensing. These data demonstrated the efficiency of the novel technology for controlling the APCI chemistry in ion mobility cells. 1-bromohexane was also dispensed into the DMS at steady-state mass fluxes from 149 - 2644 ng min\(^{-1}\). Only one product ion was observed throughout the concentration range, although the relative signal intensities of the reactant and product ions were demonstrated to be controllable. A final element to the dopant characterisation studies assessed the potential for simultaneously controlling the ionisation processes in the positive and negative modes through dispensing of a dopant mixture of 50%, 50% v/v 2-butanol, 1-bromohexane. The same ionisation processes were shown to take place as for the individual dopants (Figures 5.29 and 5.30), confirmed by using t-test statistics for the comparison of mean product ion signal intensities between the singularly-dispensed and mixed-dispersed methods. The capacity for simultaneous dopant control in the DMS cell was demonstrated in this work. Analogous to the transverse IMS studies, mass spectrometry would have been required to validate the identities of the product ions, and will be a targeted approach in future studies.

### 6.6 Analysis of 2-octanol using 2-butanol doping

The final phase of this work hypothesised that (R)-(-)-2-butanol could be dispensed as a dopant species to chirally resolve the R(-)- and S-(+) enantiomers of 2-octanol, which were introduced into the DMS cell at a fixed concentration of 52.8 µg m\(^{-3}\) via permeation sources. Chiral resolution was not observed from dispensing R(-)-2-butanol at DMS cell concentrations of 60.2 µg m\(^{-3}\) to 945.0 µg m\(^{-3}\). The reasons for this were undetermined, but could have been from insufficient differences in the clustering properties and differential mobility (\(\alpha\)-values) of the enantiomers. Alternatively, there is only the potentiality for a single point of inter-molecular hydrogen bonding interaction between 2-octanol and (R)-(-)-2-butanol (at the –OH group), which would be insufficient for chiral resolution under Pirkle’s 3-point interaction rule [136,202]. In hindsight, enantiomeric separation work may have been easier to accomplish with analytes containing several functional groups and \(\pi\)-bonding systems (e.g. alanine) to enable increased numbers of analyte-dopant interactions. Time constraints prevented this from occurring.
An alternative ion swarm to the product ions observed for 2-octanol was determined when dispensing (R)-(-)-2-butanol at a concentration of 60.2 µg m⁻³. The cluster ion appeared at a compensation voltage of -26.6 V cm⁻¹ under an RF field of 23.6 kV cm⁻¹; the monomer and dimer ions for 2-octanol were observed at -146.6 V cm⁻¹ and +26.6 V cm⁻¹, respectively. The mean intensity of the alternative ion swarm after applying background data correction was 28 mV, as opposed to 8 mV for the 2-octanol dimer ion. This demonstrated the potential of (R)-(-)-2-butanol as a dopant species for increasing the detection sensitivity in such a system, although the identity of the ion swarm could not be determined through DMS data alone.

6.7 Future Work

Concepts for introducing, calibrating and controlling dopants and their ionisation chemistries in both IMS and DMS systems using PZX dispensing have been proven in this work. Methods have also been developed to enable organic liquids with different physical and chemical properties to be optimally dispensed at predetermined concentrations into an ion mobility cell. Work is on-going to exploit the technology further by developing these proven concepts for use in actual analytical applications. Dopant/taggant combinations are currently being explored to optimise the detection of specific taggant markers present in fuel samples. The samples are expected to include multiple taggants at known concentrations, such that a chemical fingerprint of each fuel can be generated.

Consider a potential operation involving the detection of the candidate diesel taggant markers, iso-butylamine (C₄H₁₁N) and 1-iodobutane (C₄H₉I). These compounds have been determined as potential roadside test markers for determining diesel origin, and are analysable through linear drift tube IMS devices, such as the lightweight chemical detector (LCD 3.3), developed and sold by Smiths Detection, Watford, UK [203]. Work has been done to enable these markers to be detected at concentrations in the fuel matrix of 10 ppm, using a sheath-flow dynamic headspace sampling approach, analogous to the one shown in Figure 4.8. Example spectra of these candidate markers are shown in Figure 6.1. Thermal desorption devices, employing a 4-port ed, 2-way valve, and an adsorbent trap containing Tenax™ GR have been designed and developed in these applications for the purposes of enriching the marker concentration, improving the detection limits to around 100 ppb in the fuel, and for creating a desorption profile for the marker, for reducing the possibilities of false
positives and negatives. Marker enrichment by thermal desorption is cost effective as less marker is required per unit volume of fuel, and more difficult to launder, as it is better hidden within the fuel matrix.

Figure 6.1 IMS spectra of iso-butylamine (top spectrum) and 1-iodobutane, present in a diesel sample at 10 ppm(v). The spectra were obtained using an LCD 3.3 linear drift tube IMS stand-alone, portable device, interfaced to a dynamic headspace sampler using a sheath flow. The reactant ion peak (RIP) in the positive mode was present at a drift time of 5.08 ms; the product ion peak for iso-butylamine was present at 7.09 ms. In the negative mode, the RIP was present at 4.99 ms and the product ion for 1-iodobutane, 5.21 ms. These compounds were identified as potential markers for fuels in future systems.

*This work forms part of a collaborative approach with Dr. Victor Bocos-Bintintan and Professor Paul Thomas, Loughborough University.
Detection limits for these markers can be theoretically improved further by introducing dopants which either form more stable cluster ion swarms with the markers, or reduce potential background interferences from the fuel matrix. It is the intention of future studies to introduce dopants in this type of application through drop-on-demand PZX dispensing, enabled through command scripts to automate the dispensing process.

Nonylamine is the proposed dopant for the analysis of iso-butylamine, due to its relatively high PA of 941 kJ mol⁻¹. The LCD 3.3 will be subjected to nonylamine doping at the point in the temperature profile where iso-butylamine desorbs from the adsorbent trap. The doping may take the form of a transient bolus, such as that demonstrated in Section 5.4. 1-bromohexane is the proposed dopant for analysing 1-iodobutane in the negative mode. Switching of dopant chemistries is therefore an important concept in this type of analysis. The system is expected to comprise two PZX dispensers for containing the two dopants. A schematic of the proposed instrumental setup is shown in Figure 6.2. 500 µL diesel, containing ~10 ppb(v) iso-butylamine and 1-iodobutane is placed into a 20 cm³ headspace vial, surrounded in an aluminium heated chamber (A). The sampling manifold for the headspace sampler is analogous to that described in Section 4.4.2. 100 cm³ min⁻¹ filtered air (B) is used to transport the headspace vapours to a 4-port, 2-way valve (C), to which a secondary transport gas flow of 100 cm³ min⁻¹ filtered air is supplied (D) and an exhaust line (E). During sampling, the vapours are desorbed onto a Tenax™ GR (2,6-diphenylene-oxide) adsorbent trap (F), where the volatiles are concentrated. A 3-port, 2-way valve (G) connects the exit of the trap to a secondary exhaust line (H) and also interfaces to the LCD 3.3 ion mobility spectrometer (I) via an engineered PVA sampling cap and capillary tubing. A tee-union split as this interface juncture permits nonylamine and 1-bromohexane dopants to be introduced on-demand to the system through dual PZX dispensers (J), which have been built and described throughout.
Figure 6.2  A schematic of the proposed instrumental design for analysing fuel markers, incorporating PZX dispensers.
The proposed idea for the experimental sequence in this work follows four stages: sampling, desorption, detection, recovery. These are described below.

1) **Sampling (Figure 6.3)** - Fuel sample vapours containing the markers are extracted via the dynamic headspace loop for a period of 50s. The flow rate exiting the headspace sampler is 100 cm$^3$ min$^{-1}$. The 4-port valve is maintained in position 1, with the vapours transferring to the unheated (ambient temperature) adsorbent trap. A secondary clean air flow is supplied through port 3 in the 4-port valve at 100 cm$^3$min$^{-1}$, exiting through a charcoal-containing exhaust at port 4. Vapours and air exiting the thermal desorption trap are directed via a 2-way, 3-port valve at the trap exit. At the sampling stage the 3-port valve is at position 1, enabling the vapours to exit through a charcoal-containing exhaust region (termed “Exhaust 2”).

Figure 6.3 Schematic of the proposed sampling phase for analysing diesel markers. Red arrows indicate fuel vapours; green arrows represent clean air.
2) **Desorption (Figure 6.4)** – The 4-port valve is manually switched to position 2 (90° turn), allowing previously-sampled vapours emanating from port 1 to be sent to waste at exhaust 1 (port 4). Switching valve positions allows clean gas, operating at 100 cm³ min⁻¹, to pass through the thermal desorption trap, thereby creating a clean carrier gas flow. The trap is heated by applying a set current to an aluminium heating block located around the trap, at a rate of 100 °C min⁻¹, to 250 °C. The total heating process is 2:10 – 2:30. The 3-port valve at the exit to the trap is maintained at position 1, enabling the volatile fuel matrix to be sent to waste at Exhaust 2.

![Figure 6.4](image)  
**Figure 6.4** Schematic of the proposed desorption phase for analysing diesel markers. Red arrows indicate fuel vapours; green arrows represent clean air.

3) **Detection (Figure 6.5)** – The 3-port valve is manually switched to position 2, allowing the desorbed vapours to pass to the IMS inlet. This is done at the
point in the desorption temperature profile where the target marker itself desorbs. The 4-port valve is maintained at position 2 throughout this sequence. The target dopant for enhancing detection sensitivity of the fuel marker is dispensed on demand from the PZX dispenser, meeting with the marker in the IMS transport gas, just prior to the IMS cell inlet. The dispensing of the dopant can be automated as desorption temperature is proportional to heating time.

![Diagram](image_url)

Figure 6.5 Schematic of the proposed detection phase for analysing diesel markers. Red arrows indicate fuel vapours; green arrows represent clean air.

4) **Recovery (Figure 6.6)** – The 3-port valve is switched back to position 1, to allow any excess vapours to exit through the exhaust. The thermal desorption trap is cooled naturally back to ambient temperature. The 4-port valve is
maintained in position 2 to allow cleaning of the trap throughout this process. The fuel sample in the headspace vial is removed ready for the next sample analysis.

Figure 6.6 Schematic of the proposed recovery phase for analysing diesel markers. Red arrows indicate fuel vapours; green arrows represent clean air.

These descriptions are theoretical examples of work which is currently being undertaken in funded follow-on projects to work produced for this thesis. Other specific applications that will be targeted experimentally are the analysis of biomarkers or drugs for disease [204] in human tissue fluids (e.g. saliva, blood), and the analysis of toxins or drugs of performance enhancement. Many of these applications would involve pre-separation by GC, and involve the analysis of multiple analytes, requiring a range of dopants. A means for successfully detecting trace compounds in complex biological tissues, for example, may involve a primary gas chromatographic separation stage, followed by targeted dopant dispensing to
optimise biomarker or drug detection on a time-scale compatible with the elution of that specific analyte.

Miniaturisation of the PZX technology for commercial or in-field use is another natural progression to the current work. To achieve this, the interface design and parameters (pressure, temperature) must be optimised, and therefore studies must be developed to enable a greater understanding of the systems. A particular area for focused work will be investigating in detail the effects of turbulent air currents around the dispenser nozzle. This was found in the current studies to be a limiting factor for controlling dopant concentration in the ion mobility cell. Another area of necessary work for automating dispensing procedures will be the development of sensors which can optimise the PZX waveforms. This could be enabled via acoustic sensors attached to the interface manifold that measures variations in resonance frequencies and amplitudes of the dispensed droplets. Dopant vapour concentration control in fieldable PZX-IMS instruments may be accomplished through digital mass flow controllers, manipulated though software control.

The PZX technology offers advantages as a novel sample introduction technique for IMS and other analytical instrumentation. Sample sizes in terms of mass ranging from ng to mg can be programmed to be delivered on demand with negligible sample loss. The relatively high sensitivity and low linear ranges of ion mobility spectrometers (see Section 2.1) make pico-PZX dispensing a particularly suitable technology for introducing liquid samples at masses compatible with IMS analyses. Analysis of samples with high viscosities or complex matrices may suffer from blockage of the dispensers, however, due to typical orifice sizes of 20-80 µm. Sample preparation may or may not be required depending on the chemical composition of the sample. A further advantage of the current technology is the rapid generation of vapours that can be used to calibrate IMS responses. Generating known vapour masses from a PZX dispenser using standards could be a future method for calibrating the concentrations of analytes. The procedure would not require preparation of different concentration standards, as the dispenser could be programmed to deliver various masses through boluses at a fixed number of droplets. Other analytical techniques that could benefit from interfacing a PZX dispenser to deliver samples are direct injection mass spectrometry techniques, and inductively coupled plasma (ICP) spectrometry. The technique has already been used [16] as a sample introduction method for GC coupled with flame ionisation detection (see Section 2.6.2).
The coupling of mass spectrometers to verify the ionisation processes discussed in Sections 5.5 and 5.6 is a natural progression to this work. This is to be employed in proposed future studies where knowledge of the ionisation processes is required for understanding dopant/taggant interactions in more complex systems such as fuel samples. Studies are also continuing to increase method libraries for optimising the dispensing procedures of other candidate dopants.

The ability of the current technology to rapidly generate liquids and vapours of known masses at the nanogram level could have future uses outside the field of chemical analysis. Recent advancements and interest in lab-on-a-chip technology makes the production of such material an attraction for formulating chemical reactions on substrates. An example could be the generation of antigen/antibody complexes used in preparing bioaffinity assays. Work is ongoing to develop novel printed circuit boards by piezoelectrically dispensing complex polymers in specific orientations onto dielectric substrates [6].

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