In-Situ Mass Spectrometry Analysis Under Ambient Conditions

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By

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Abstract

Mass Spectrometry (MS) is an important analytical tool in the identification and quantification of a wide range of samples, primarily because of its speed, sensitivity, selectivity and versatility in analysing, gases, solids and liquids. MS is an interdisciplinary analytical tool, impacting many areas of science from physics, through chemistry, to biology. However MS is mainly limited to laboratory settings due to the high vacuum requirement needed for ion generation and processing. The main theme of this work is the development of ionisation methods that enable ion generation and processing under ambient conditions in the open air outside of the laboratory for *in-situ* applications. To that end, it is also important that ions are generated and processed with little or no extensive sample preparation steps required.

In this work the development of two ambient ionisation methods: desorption atmospheric pressure chemical ionisation (DAPCI) and paper spray (PS) ionisation and their application for *in-situ* MS analysis is demonstrated. A DAPCI handheld ion source version based on DAPCI was developed to ignite a corona discharge in air and operates for up to 12 h continuously using only 12 V battery. Both DAPCI and PS ambient ionisation methods were implemented for *in-situ* MS analysis and were used to detect trace amounts (< ng) of different classes of chemical compounds (i.e hydrocarbons, explosives corrosion inhibitors and metaldehyde in waters samples); this was achieved rapidly (i.e. less than 1 minute) with little or no sample preparation in the open air. Both ambient ionisation methods (i.e., DAPCI and PS) were used with either a commercial instrument or with a custom miniature mass spectrometer to identify and characterize traces amounts of petroleum oil hydrocarbons and additives (e.g. quaternary ammonium corrosion inhibitors), and water pollutants (e.g.

metaldehyde) with high sensitivity and selectivity. The handheld DAPCI and PS methods were also applied to the *in-situ* direct analysis of explosives. Good performance was achieved with the miniaturised instrument giving detection limits within an order of magnitude to those achieved using a benchtop commercial instrument. The results reported in this thesis should be of importance to those interested in ambient ionisation mass spectrometry, miniature mass spectrometry, *in-situ* MS analysis, oilfield chemical analysis, homeland and border security agencies and environmental monitoring.

Since we are assured that the all-wise Creator has observed the most exact proportions, of number, weight and measure, in the making of all things, the most likely way therefore, to get any insight into the nature of those parts of the creation, which come within our observation, must in all reason be to number, weigh and measure.

Vegetable Staticks, by Stephen Hales, (17 Sep 1677– 4 Jan 1761)

The Lord is gracious and righteous; our God is full of compassion. The Lord protects the simple-hearted; when I was in great need, he saved me. Be at rest once more, O my soul, for the Lord has been good to you. For you, O Lord, have delivered my soul from death, my eyes from tears, my feet from stumbling, that I may walk before the Lord in the land of the living.

Psalm 116: 5-9

To Jesus Christ; my Savour and Lord Be the Glory now and Forever!
-Amen-

Acknowledgements

"I will sing to you my Lord, because you have dealt bountifully with me". Much thanks and praise is due to you my Lord and Saviour Jesus Christ, for your steadfast love towards me every micro second of this PhD process. You alone are; “my rock, salvation and my fortress, I will never be shaken!” My Lord Jesus Christ you are indeed the source of my strength and brought me through this time of PhD study.

Next I would like to recognise my immediate, extended family and special friends. I would like to thank my late uncle (Duncan Kibaya) and his wife Mary Kibaya for their love and pastoral care, and all they sacrificed to make sure that I get an education. For that I will always be grateful. Special mention and thanks to Taata Katerega John, Taata Mutebi Ronald and Taata Lukanga, Mr and Mrs Stephen and Diana Luswata Kajambiya for their ever encouraging words and help. To Jjaaja Nakito and Bena Nakawooya for their special care and love. My special brothers and sisters; Mr. and Mrs. Robert and Katherine Davies, Mukisa Kibaya and sons, Dr. Simon Maher and his wife Amy, Mr. Graham Douglas Swift, Dr. Abraham Baddu, Dr. Adris Ajia, Mr. and Mrs. Tim and Sarah Crow, Dr. Jonathan and his Katherine Room, and Ssalongo Paul Kasule Sekabuuza, for standing with me through thick and thin. Special thanks are due to all my extended family all over world. I know they were praying for me all the time.

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will achieve great things; I love you so much. To Beggs, the love of my life, a life companion, I love you completely.

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I'm indebted to Prof Graham R. Cooks, who helped and introduced me to the field of mass spectrometry; his guidance and direction have proved invaluable. He always made me aware of different ways to further my research abilities as a scientist. For that I will forever cherish my time in Aston Labs Department of Chemistry Purdue University. I also had a great opportunity to work and train with several world renowned scientists (Dr Anyin Li. W.S. Mike, Prof Xin Yan, Dr. Pu Wei, Dr. Josh Wiley). I owe my sincere gratitude to Prof Abraham who taught me how to use a mass spectrometer and all the gas phase (ion/molecule reactions) chemistry; this involved I had a steep learning curve in the field of ion/molecule reactions.

Special thanks are due to Prof. Dr. Stephen Taylor, my academic advising professor; his breadth of knowledge and unique ability to communicate both verbally and written. Prof. Taylor Steve my hat is off, thank you very much for taking me through this process. I want to thank all the mass spectrometry present and past members (Maria Juno, David McIntosh, Dr. Boris, Dr. Sarfraz and Dr. Stimatious). It has been a privilege to work with you all and I look forward to future collaboration.

There is always someone in a group who is the go-to person to find answers, Prof. Simon fits this bill. I can't count how many times Prof Simon pointed me in the right direction. Special countless scouser thanks are due to Prof. Simon Maher.

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Abbreviations

AI-MS	Ambient Ionisation Mass Spectrometry
APCI	Atmospheric Chemical Ionisation
CE	Capillary Electrophoresis
CI	Chemical Ionisation
CID	Collision Induced Dissociation
DART	Direct Analysis in Real Time
DESI	Desorption Electrospray Ionisation
DF	Double Focusing
DOF	Distance of Flight
DAPCI	Desorption Atmospheric Pressure Chemical Ionisation
EI	Electron Ionisation
ESI	Electrospray Ionisation
ET	Electron transfer
EU	European Union
FAB	Fast-Atom Bombardment
FD	Field Desorption
FIFA	Fédération Internationale de Football Association
FTICR-MS	Fourier Transform Ion Cyclotron Resonance Mass Spectrometer
FWHM	Full-width at half-maximum height
GC	Gas Chromatography
HR	High resolution
ICR	Ion Cyclotron Resonance
IMS	Ion mobility Mass Spectrometry
IMS	Imaging Mass Spectrometry
IS	Internal Standard
LC	Liquid Chromatography
LoD	Limit of detection
m/z	Mass to charge ratio
MS	Mass Spectrometry
MS^n	Multiple stage mass spectrometry
MALDI	Matrix Assisted Laser Desorption/Ionisation
MIMS	Membrane Inlet Mass Spectrometry
Mw	Molecular Weight
MS	Mass Spectrometry
MS^n	Tandem Mass Spectrometry
MS/MS	Tandem Mass Spectrometry
ppb	Parts per billion
ppm	Parts per million
PS	Paper Spray
QIT	Quadrupole Ion Trap
QMS	Quadrupole Mass Spectrometer
QQQ	Triple Quadrupole Mass Spectrometer
Q-TOF	Quadrupole Time of Flight

RF	Radio frequency
S/N	Signal-to-noise ratio
SIMS	Secondary Ion Mass Spectrometry
SPE	Solid Phase Extraction
SWIFT	Stored Waveform Inverse Fourier Transform
TOF-MS	Time of Flight Mass Spectrometer
VOC	Volatile organic compound
WADA	World Anti-Doping Agency

Symbols

a	Mathieu stability parameter
B	Magnetic field intensity
da	dalton, an atomic mass unit, commonly used in biochemistry for the mass of ions and molecules
e	Charge on electron
E	Electric field intensity
f	Frequency of rf supply
Th	thomson (The name of an *m/z* unit or increment)
L	Length of analyser electrodes
m	mass [Da]
m/z	mass-to-charge ratio (where z is numerically equivalent to e, the mass of the electron, which is 9.109×10^{-28} g)
N	Number of rf cycles
q	Mathieu stability parameter
r	Radius of the analyser electrodes
r0	Inscribed electrode radius
rf	Radio Frequency
rie	Ion source exit radius
t	Time
U	Direct potential
V	Alternating potential
v	Ion velocity
Vion	Nominal ion source accelerating voltage
x0	Initial displacement of ion from *x*-axis
xmax	Maximum displacement of ion from *x*-axis
y0	Initial displacement of ion from *y*-axis
ymaz	Maximum displacement of ion from *y*-axis
z	Charge number
Δm	Mass spectral peak width
ξ	Modified time parameter
ϕ	Electric potential
ω	Angular frequency of rf supply

Overview of Chapters

This thesis presents the development and application of two novel ambient ionisation methodologies; (i) desorption atmospheric pressure chemical ionisation (DAPCI), and (i) paper spray ionisation (PS) coupled to a miniature mass spectrometer for *in-situ* chemical analysis. The motivation behind this work is to extend the utility of mass spectrometry analysis beyond the laboratory environment. The foremost advantage is the provision of data in real-time (or near real-time) at the point of interest allowing key management decisions to be taken in a timely manner. Subsidiary advantages relate to the economic and effective criteria. By effectively taking the lab to the sample rather than the sample to the lab, the sample integrity is maintained and sampling/handling costs significantly reduced. As such the DAPCI and PS ambient ionisation methods have therefore been applied to the direct analysis of a wide range of samples *"in-situ* at source" using both conventional and portable mass spectrometers, in each case with little or no sample preparation. Here, a brief overview of the contents of each chapter is given.

***Chapter* 1** this chapter comprises literature review that outlines a historical overview of the major instrumentation achievements that have driven mass spectrometry forward in the past century. Scientific progress is usually made via the cumulative effort of a large number of researchers. As such an introduction to mass spectrometry (MS), an overview of some key applications of MS, and the current and future trends of mass spectrometry are given. This chapter has been published as a colloquium review article in Review of Modern Physics Journal (S. Maher, Jjunju.

Fred. P. M, and S. Taylor; “Colloquium: 100 years of mass spectrometry: Perspectives and future trends” Rev. Mod. Phys. 2015 87, pp. 113-135).

***Chapter* 2** describes the application of desorption/ionisation techniques desorption atmospheric pressure chemical ionisation mass spectrometry (DAPCI-MS) for the direct analysis of condensed phase hydrocarbons utilizing an extensive array of hydrocarbons with differing functionality and little or no sample preparation under ambient conditions. In this chapter the DAPCI-MS ionisation mechanism is presented together with interesting variations of the ionising species that can be attained; this adds versatility to the system and presents the two separate DAPCI ionisation mechanisms (proton transfer and electron abstraction reactions) that could be applied for selective ionisation. This work has been published and presented at international conferences (i.e. Jjunju. Fred. P. M, *et al.* “Ambient analysis of non-basic nitrogen compounds in petroleum oil using desorption atmospheric pressure chemical ionisation”, Prepr. Pap.-Am. Chem. Soc., Div. Energy Fuels. 59, (2), pp. 753-755 (2014), Jjunju, F. P. M. Jjunju, *et al*, Ambient analysis of nitrogen compounds in petroleum oil using desorption atmospheric pressure chemical ionization, RSC Chemistry in the Oil Industry XIII Symposium, Manchester, UK (November 2013), Fred P. M, *et al.* "Hydrocarbon analysis using desorption atmospheric pressure chemical ionisation." International Journal of Mass Spectrometry 345 (2013): 80-88).

***Chapter* 3** describes a methodology for the direct *in-situ* detection of alkylated benzenes and polyaromatic hydrocarbons (PAHs) using the DAPCI ionisation technique coupled to a portable mass spectrometer. The ionisation mechanism and fragmentation patterns were also investigated for different PAHs and alkylated benzenes. The results showed that different PAHs and alkylated benzenes can easily be ionised and detected by this method. The combination of DAPCI with a portable

mass spectrometer may find more important applications for *in-situ* analysis of these compounds as well as other organic compounds in real environmental samples. This work has been published in the “Harsh Environment Special Issue” of American Journal of Mass spectrometry (Jjunju, Fred P. M, et al. "Analysis of Polycyclic Aromatic Hydrocarbons Using Desorption Atmospheric Pressure Chemical Ionisation coupled to a Portable Mass Spectrometer." Journal of the American Society for Mass Spectrometry 26.2 (2015): 271-280).

***Chapter* 4** describes the design and development of a novel truly solvent and gas cylinder free handheld ion source for onsite point and shoot applications, based on DAPCI. The developed handheld source was used to interrogate nitroaromatic explosive formulations instantaneously from a surface in open air without any sample preparation in the open environment. The analytical capability of this ion source was demonstrated by detecting trace of levels of individual nitroaromatic explosives in amounts as low as 5.8 pg with a linear dynamic range of at least 10 (10 to 100 pg) with a relative standard deviation (RSD) of ca. 7% and with an R^2 value of 0.9986. This work has been published in the Analytical Chemistry (Jjunju, Fred P. M, et al. "Hand-Held Portable Desorption Atmospheric Pressure Chemical Ionisation Ion Source for *in-situ* Analysis of Nitroaromatic Explosives." Analytical chemistry 87.19 (2015): 10047-10055").

Chapter 5 describes the implementation of paper spray mass spectrometry for the *in-situ* analysis of anti-corrosion additives and pesticides (metaldehyde) and illicit drugs in complex petroleum and water samples matrixes. This methodology is an important capability for the direct analysis of additives in real samples for on-site applications. The experiments were performed using both a commercial bench-top instrument and a portable miniature mass spectrometer. Direct analysis of samples

without any pre-treatment is an important area of analytical mass spectrometry. This method can provide almost instantaneous data while minimizing sample preparation prior to MS analysis. Because no prior sample treatment is required, both cost savings and simplicity of analysis are considerably increased. This work was published in the following journals; (i) RCS Analyst Journal (Jjunju, Fred P aul Mark, et al. "*Insitu* analysis of corrosion inhibitors using a portable mass spectrometer with paper spray ionisation." Analyst 138.13 (2013): 3740-3748, (ii) Jjunju, Fred P. M, et al. "Rapid Screening and Quantification of Aliphatic Primary Alkyl Corrosion Inhibitor Amines in Water Samples by Paper Spray Mass Spectrometry," Analytical Chemistry (2016). A further paper has been submitted to nature scientific reports; (iii) Simon Maher, Fred. P. M. Jjunju, Deidre E. Damon, Yosef S. Maher, Safaraz U. Syed, Ron M. A. Heeren, Iain S. Young, Stephen Taylor and Abraham K. Badu-Tawiah. "Direct Analysis and Quantification of Metaldehyde in Water using Reactive Paper Spray Mass Spectrometry" "2016, Submitted to Nature Scientific reports, (iv) A. Li, F. P. M. Jjunju, S. Taylor and R. G. Cooks, In-situ analysis of oil matrices using paper spray ionization and portable mass spectrometer: toward chemical analysis in the oil field of corrosion inhibitors and so on, RSC Chemistry in the Oil Industry XIII Symposium, Manchester, UK (November 2013).

Chapter 6 summarises the major contributions from the work presented and gives some suggestions for future work.

Overview of Author Contributions

The work presented in this thesis would not have been possible without the help and input of a talented group of scientists, many of whom are co-authors on the journal articles that have been published or are in review. Identified below are the individual contributions of my co-authors towards the work presented herein.

Chapter 1 provides a literature review covering the historical developments and major instrumentation achievements that have driven mass spectrometry forward in the past century with a succinct overview of the major applications of modern mass spectrometry. Linked to this chapter is a publication written by the thesis author and Dr. Simon Maher with contribution from Prof Stephen Taylor. The author was responsible for writing several sections of the published manuscript, assembling figures and reviewing the overall manuscript throughout the submission process.

***Chapter* 2** describes the application of desorption/ionisation techniques desorption atmospheric pressure chemical ionisation mass spectrometry (DAPCI-MS) for the direct analysis of condensed phase hydrocarbons utilizing an extensive array of hydrocarbons with differing functionality with little or no sample preparation under ambient conditions. The initial concept was devised by me with assistance from Prof Stephen Taylor (my supervisor) and Prof Graham Cooks (our collaborator), I performed all the experiments with Dr Simon Maher, Dr. Anyin Li, Dr Abraham Badu, Dr. S. Santosh (a former graduate student at Purdue University Department of Chemistry) and Dr Iman Roqan also helped with instrument training and some experiments. I wrote all the text and prepared all figures for the manuscript. Prof. R.

Graham Cooks, Dr. Simon Maher and Prof Stephen Taylor reviewed the final manuscripts. This work has been published in Prepr. Pap.-Am. Chem. Soc., Div. Energy Fuels. 59, (2), pp. 753-755 (2014), and Jjunju, Fred P. M, *et al.* "Hydrocarbon analysis using desorption atmospheric pressure chemical ionisation." International Journal of Mass Spectrometry 345 (2013): 80-88).

***Chapter* 3** describes a methodology for the direct *in-situ* detection of alkylated benzenes and polyaromatic hydrocarbons (PAHs) using DAPCI ionisation technique coupled to a portable mass spectrometer. The experimental work, including the design, execution and data analysis, was carried out by me (the first author). The article was written by the author with contributions from Prof Stephen Taylor, Prof Graham Cooks and others. Dr Simon Maher (former graduate student department of EE&E University of Liverpool), Dr. Anyin Li, Dr Abraham Badu, (a former graduate students at Purdue University Department of Chemistry) also helped with instrument training and some experiments. This work has been published in the "Harsh Environment Special Issue" of American Journal of Mass spectrometry (Jjunju, Fred P. M, et al. "Analysis of Polycyclic Aromatic Hydrocarbons Using Desorption Atmospheric Pressure Chemical Ionisation coupled to a Portable Mass Spectrometer." Journal of the American Society for Mass Spectrometry 26.2 (2015): 271-280).

***Chapter* 4** describes the design and development of a novel truly solvent and gas cylinder free handheld ion source for onsite point and shoot applications, based on DAPCI. The design, fabrication, experimental work, including the miniature handheld DAPCI ion source chemical and electrical characterization, calibration, the coupling of the DAPCI source to the MS and sample preparation, was carried out by the author, with contribution from Dr. Simon Maher, Mr Barry Smith, Dr Safraz Sayed, and Prof Stephen Taylor. The article was written by the author with contributions. The final

manuscript was reviewed by Prof. Ron Hereen, Prof Graham Cooks, and Dr Anyin Li and Prof Stephen Taylor. This work has been published in the Analytical Chemistry (Jjunju, Fred P. M, et al. "Hand-Held Portable Desorption Atmospheric Pressure Chemical Ionisation Ion Source for *in-situ* Analysis of Nitroaromatic Explosives." Analytical chemistry 87.19 (2015): 10047-10055").

Chapter 5 describes the implementation of paper spray mass spectrometry for the *in-situ* analysis of anti-corrosion additives and pesticides (metaldehyde) and illicit drugs in complex petroleum and water samples matrixes. The experimental design, paper spray ion source calibration, coupling of paper spray to the MS and sample preparation, was carried out by the author. Dr. Simon Maher, Miss. Deidre E. Damon, Dr. Richard M. Barrett, S. U. Syed, Ron M. A. Heeren Li, Dr Abraham Badu, Dr. Iain Young, Pu Wei, Lifan Li, Dr. Iman Roqan, Prof Z. Ouyang, and Prof Cooks helped in the instrument setup and training while Prof Stephen Taylor supervised the work. This work was published in the following journals; (i) RCS Analyst Journal (Jjunju, Fred P aul Mark, et al. "*In-situ* analysis of corrosion inhibitors using a portable mass spectrometer with paper spray ionisation." Analyst 138.13 (2013): 3740-3748, (ii) Jjunju, Fred P. M, et al. "Rapid Screening and Quantification of Aliphatic Primary Alkyl Corrosion Inhibitor Amines in Water Samples by Paper Spray Mass Spectrometry," Analytical Chemistry (2016). A further paper has been submitted to Nature scientific reports; (iii) Simon Maher, Fred. P. M. Jjunju, Deidre E. Damon, Yosef S. Maher, Safaraz U. Syed, Ron M. A. Heeren, Iain S. Young, Stephen Taylor and Abraham K. Badu-Tawiah. “Direct Analysis and Quantification of Metaldehyde in Water using Reactive Paper Spray Mass Spectrometry” “2016, (submitted to Nature Scientific reports). The article was written by the author with contributions

from all the co-authors. All the authors revised the final manuscripts that were published or are submitted for publication.

Declaration Statement

I declare that this thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at the University of Liverpool or at any other institution.

The following papers form a small part of my thesis in chapter 2 and 5, were published in May 2013 prior to registration for my PhD program in July 2013, but have not been submitted towards any other qualification at any other institution; (1) Jjunju, Fred P. M, *et al.* "Hydrocarbon analysis using desorption atmospheric pressure chemical ionisation", International Journal of Mass Spectrometry 345 (2013): 80-88), (2) Jjunju, Fred Paul Mark, et al. "*In-situ* analysis of corrosion inhibitors using a portable mass spectrometer with paper spray ionisation." Analyst 138.13 (2013): 3740-3748. These papers form a small part of the body of chapter 2 and 5, they have been included because they form the basis of my PhD research.

Chapter 1 : Introduction

1.1 Overview

Mass spectrometry (MS) is a powerful analytical technique with high sensitivity and specificity for identifying, quantifying, and exploring molecular structures of unknown compounds [1]. This can be done even in the presence of hundreds of compounds in complex mixtures. Since its invention a century ago by Nobel laureate Sir J. J Thompson, MS has become a subject area of enormous scope. MS is an invaluable analytical tool for a wide range of professionals including, physicists, chemists, biologists, physicians, astronomers, geologists, archaeologists, physiologists and material scientists [1]. Mass spectrometers are utilised in a wide range of applications in the chemical, electronics, food processing, petroleum, and pharmaceutical industries etc. They are routinely used in the following applications: (i) in the confirmation of the identity of known compounds (e.g. compounds from target synthesis, metabolites, compounds extracted from a sample matrix), (ii) to identify unknowns (iii) to assess the degree of isotope incorporation in labelling studies, (iv) as a detector linked to a chromatographic system for quantitative and qualitative analysis, (v) in the accurate mass measurements for the determination of molecular formulae, (vi) in fundamental studies of the physical chemistry of ions [2-6].

Mass spectrometers are deployed in environments as diverse as the ocean depths, here on earth for identifying trace chemicals [7], and also in space for extra-terrestrial exploration [8, 9]. A mass spectrometer is an instrument used to separate

charges gas phase species according to their mass (*m*) and charge (*z*) ratio (*m/z*) under a vacuum. A computer is always used to control the mass spectrometer and data processing.

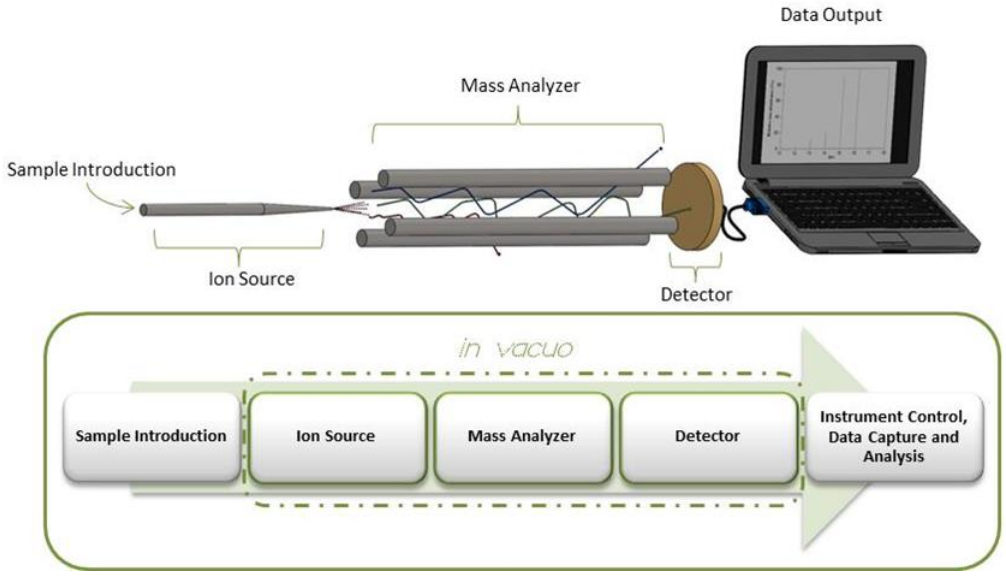

Figure 1.1: Mass Spectrometry Analysis stages

In a typical MS experiment, the sample to be analysed is first introduced into the vacuum system of the MS instrument using an appropriate sample instruction system. In the ion source region, neutral molecules are ionised and then transported into the mass analyser. This is usually a region of low pressure (~10^{-4} to 10^{-8} Torr) in which the ions are separated according to their *m/z* ratio, using either electric or magnetic fields or a combination of both. After the ions are separated they are detected and the generated signal is processed and displayed to the user as a mass spectrum. Figure 1.1 shows the typical key steps of MS analysis.

The analytical scientist usually has to select the compatible/appropriate sample inlet, ionisation method and the mass analyser. What is "compatible/appropriate" will depend on the nature of the sample being analysed. MS is an extremely versatile analytical technique, as created ions can also be broken

down and mass-sorted again using tandem MS or "MS/MS" to provide more information on individual compounds with greater specificity [10]. In most cases, the ion is fragmented through the addition of energy into the mass selected ion by colliding it with a neutral gas, (i.e. collision induced dissociation or (CID)).

The MS/MS experiment enables multiple stages of MS to be carried out. In the first stage of MS/MS, ions of a desired *m/z* are isolated from the rest of the ions emanating from the ion source. These isolated ions (termed parent ions or precursor ions) are then induced to undergo a chemical reaction that changes either their mass (*m*) or charge (*z*). Typically, the reactions involve some type of process to increase the internal energy of the ions of interest, leading to dissociation. The ions resulting from the various chemical reactions are termed product ions, and these are analysed with the second stage of MS/MS.

A mass spectrum is a plot of relative abundance (signal intensity) versus *m*/*z* on the abscissa. This plot can be used in the determination of the molecular weight of a compound and the elucidation of elemental composition, structural information and isotopic abundances of the compounds in a sample. There are various types of mass spectrometer and they are usually differentiated based on the method of mass analysis (and hence the physical principle of operation) that the instrument uses.

Magnetic sector instruments use momentum as a separation principle. They generally use a combination of electrostatic and magnetic fields and can operate as low and high resolution instruments. Magnet sector instruments operate with high voltages on the ion source (typically 5- 10 kV).

Quadrupoles use a combination of RF (radio frequency) and DC (direct current) voltages. They are generally low resolution instruments and operate at relatively low voltages (<500 V). Quadrupoles are capable of fast scanning, hence

are ideally suited for interfacing to a wide range of sample inlets (e.g. gas/high performance liquid chromatography (GC/HPLC).

Time of flight (TOF) instruments measure the time an ion takes to travel a specific distance after acceleration by a high potential. Different mass ions of the same charge travel at different speeds. Combinations of most analysers are possible and allow 'tandem MS' (hybrids) or MS/MS to be performed. Ion trap instruments are ion trapping quadrupole instruments (QIT). In such mass analyser configurations, ions are produced and stored in the trap and progressively ejected by increasing the rf voltage. The trapped ions can be induced to undergo dissociation and hence generate a product ion spectrum within the one analyser. The majority of ion traps are benchtop instruments used for routine analysis.

Fourier transform ion cyclotron resonance (FT-ICR) mass analyser is a type of ion trap where frequencies of the circulating ions are measured and a Fourier transform is performed to give the mass spectrum. Another new type of ion trap is the orbitrap. Unlike the conventional ion traps, the orbitrap uses only electrostatic fields to confine and to analyse injected ion populations. Since its introduction in 2000 by Dr Makarov, the orbitrap has proven to be a robust mass analyser that can be used to routinely deliver high resolving power and mass accuracy. The specifications and attributes of the main types of mass analysers are summarized in Table 1.1.

Mass analyzer	**Measures**	**Upper *m/z***	**Resolution (R)$^{+}$**	**Accuracy^{++} (ppm)**
Magnetic Sector	Momentum	10^4	10^2 - 10^5	1-5
Electrostatic Sector	Kinetic Energy	10^4	10^2 - 10^5	1-5
Quadrupole,	Path Stability	10^3	10^2 – 10^4	100
Quadrupole Ion Trap (QIT)	Resonance Frequency	$>10^3$	10 – 10^4	50-100
Fourier Transform Ion Cyclotron Resonance (FT-ICR)	Orbital	$>10^4$	$>10^6$ at *m/z* 100	<1
Orbitrap	Axial Frequency	$>10^4$	6 x $>0^4$ at m/z 400	< 1ppm with a lock mass
Time-of-Flight (TOF)	Flight time	$>10^4$	$>10^4$	5-500

+ According to the IUPAC definition for resolution in mass spectrometry R = m/mΔ (mΔ is the resolving power and m is the mass of the (second) peak.

++ The difference between mean of set results or an individual result and the value that is accepted as the true value for the quantity measured

Table 1.1: Typical specifications and Attributes of main types of mass analysers.

Most ions are analysed in the vacuum of the mass spectrometer, hence, the most important process in MS is the one that converts analyte(s) of interest into gas phase ions (ionisation). The sensitivity and selectivity of any mass spectrometer crucially depends on the ionisation step. For many target compounds in any sample, their chemical properties (i.e. polarity, solubility and volatility) can be exploited such that they can be selectively ionised, whereas extraneous molecules in the sample matrix are not.

The principal factors that affect the choice of ionisation method are; the polarity, relative molecular mass and thermal stability of the analyte(s) of interest. If a compatible ionisation source is not selected then either no mass spectrum or poor quality spectrum is likely to be obtained. Most samples can be first analysed in the positive ion mode; however, the negative ion mode can also be useful particularly

when the negatively charged molecule is more stable than the corresponding positively charged one. Mass analysis in the negative ion mode may also provide complementary structural information through different fragmentation processes. In general a 'hard' ionisation process, such as electron ionisation, can produce many fragment ions and possibly poor relative ion abundance of the molecular species. However, a 'soft' ionisation process, such as electrospray ionization (ESI), produces few fragment ions with highly abundant relative molecular ion species. ESI is classified as a soft ionisation source, in that it forms ions with very low internal energies; hence in-source fragmentations are commonly inhibited.

In addition to being a softer ionisation method, ESI has some very impressive attributes such as multi-charging that allow it to be used for a wide range of analyte(s) with no limitation on the mass range. Table 1.2 outlines a summary of a few of the commonly used ionisation methods for molecular MS analysis. Other methods not shown in Table 1.2 include fast atom bombardment (FAB), liquid secondary-ion mass spectrometry (LSI-MS) (both similar to MALDI), field desorption/field ionisation (FD/FI) used for non-volatile molecules instead of EI/CI.

During the early stages of mass spectrometry development, electron impact (EI) was the first molecular ionisation method that was used to create gas-phase ions for a wide range of organic molecules. It creates positive ions due to electron ejection from the sample. EI ion source employs a tungsten filament that can be resistively heated to emit electrons under a high vacuum ($>10^{-5}$ Torr).

	Ions formed in a Vacuum		Ions formed at AP	Ions formed at atmospheric pressure		
Ionisation Method	Electron Ionisation (EI)	Chemical Ionisation (CI)	Matrix-Assisted Laser Desorption/Ionisation (MALDI)	Electrospray Ionisation (ESI)	Atmospheric Pressure CI (APCI)	Desorption Electrospray Ionisation (DESI)
Sample(s)	Non-polar and Moderately polar	Non-polar and Moderately polar	Polar and Ionic	Highly basic and acidic	Highly basic and acidic	Highly basic and acidic
Sample Phase	Gas	Gas	Solid, Liquid	Liquid	Liquid	Solids, Liquid, Gas
Sample Inlet	A probe or *via* a GC column	A probe or *via* a GC Column	Samples needs to be applied in a compatible matrix	Sample must be dissolved in a compatible solvent	Sample must be dissolved in a compatible solvent	Sample must be dissolved in a compatible solvent
Solvents used	Volatile Non-polar solvent.	Volatile Non-polar solvent	Solvents from which sample will form crystalline mixture with matrix	Mixture of water/organic solvents or acid	Mixture of water/organic solvents or acid	Mixture of water/organic solvents or acid
Ionisation Mechanism	Loss of electron forming radical cation	Ion molecule reaction with ionised reagent gas (proton transfer and cation attachment in +ve ion mode and electron capture in the –ve)	Radical cation , or Proton transfer in +ve ion and electron capture or loss of proton in -ve ion	Ion molecule reaction with ionised reagent gas (proton transfer and cation attachment in +ve ion mode and electron capture in the –ve)	Ion molecule reaction with ionised reagent gas (proton transfer and cation attachment in +ve ion mode and electron capture in the –ve)	Ion molecule reaction with ionised reagent gas (proton transfer and cation attachment in +ve ion mode and electron capture in the –ve)
Ionisation Agents	Energetic electrons	Reagent gas phase ions	Energetic Photons, plasma	Highly energetic charged droplets	Highly energetic charged droplets	Highly energetic charged droplets
Fragmentation	High energy process (high fragmentation)	Less fragmentation (original molecule is observed)	Low energy process (little or no fragmentation)	Low energy process (little or no fragmentation)	Low energy process (little or no fragmentation)	Low energy process (little or no fragmentation)
Hard or Soft *	Hard	Soft	Soft	Soft	Soft	Soft

**Soft" ionisation refers to the formation of a large proportion of ions without breaking chemical bonds. Whereas, "hard" ionisation results in chemical bonds being broken and formation of a large proportion of fragment ions.*

AP = Atmospheric Pressure

Table 1.2 : Ionisation methods commonly used for molecular MS analysis.

The emitted electrons are accelerated to interact with molecules in a vapour phase forming gas-phase ions. Because of the short lived vertical transitions associated with EI, significant extensive fragmentation of the analyte(s) is always observed [11]. Extensive fragmentation can obscure molecular weight information. Due to this characteristic, the EI ion source is commonly known as a “hard ion source".

Hard ion sources can be used to produce characteristic fragmentation patterns and this can be used to elucidate the chemical structure of a given analyte(s). On the contrary, extensive fragmentation may result in non-unique mass spectra, and can be uninterpretable when multiple analyte(s) cause overlap of fragmentation peaks. As such, it is always significantly difficult to determine the molecular weight information of analyte(s) from the EI mass spectra. This is due to the fact that EI ion source produces ion species with a wide range of internal energies, with few ions in the low energy region that yield intact molecular radical cations. The problem of extensive fragmentation was later solved with the arrival of chemical ionisation (CI) [12]. CI employs gas-phase ion/molecule chemical reactions to ionise molecules through a variety of pathways such as electron transfer, electron capture, proton transfer, cation adduction, and hydride abstraction reaction.

At high pressure, the sensitivity of CI sources is enhanced due to the increased number of gas phase collisions. Regardless of the exact ionisation mechanism employed in a CI ionisation source, collisions are adiabatic in nature. Unlike EI, lower internal energy is deposited in the samples resulting in fewer fragmentations. The most commonly used ionisation processes for both EI and CI occur in two discrete steps: (i) the sample is first volatilized and (ii) then ionised. This approach to ionisation limits the types of analyte(s) that can be analysed in the

intact form to relatively low-molecular-weight compounds that are thermally stable [13-14].

Currently it is now possible to perform MS analysis on most biological molecules. This is the case even when the target analytes are present in highly complex chemical matrixes. This breakthrough was made possible mostly due to the development of revolutionary new ionisation methods (i.e. electrospray ionisation (ESI) and matrix assisted laser desorption ionisation (MALDI)). These new ionisation methods can be used to analyse a wide range of molecules with a large diversity of size and polarities [13-14]. These ionisation methods increased the molecular-weight range of MS by orders of magnitude (i.e., up to the mega Dalton (MDa) range) making it possible to ionise a wide variety of compounds including large molecular weight biomolecules that had previously been proven difficult to analyse [15,16]. This paved the way for a MS resurgence, making it one of the most popular and powerful tools in analytical science today. Both of these ionisation techniques (ESI and MALDI) have garnered success as a result of their capacity for "soft ionisation", enabling the ionisation of large organic and biological molecules with little or no fragmentation. These ionisation methods are 'soft' (i.e., they deposit little internal energy into the sample) and induce little/no fragmentation increasing the abundance of the molecular ion.

This breakthrough towards making MS simple and versatile was no doubt made possible by the introduction of ESI and MALDI to the mass spectrometry community. Both ESI and MALDI were introduced in 1989 by Nobel Prize winners Prof J.B Fenn (for the development of ESI) and Dr Tanaka (for the development of MALDI).

The ESI ionisation method involves spraying relatively pure solutions containing analyte(s) through a capillary (20-250 μm ID) held at a high voltage (1 to 5 kV) to form micro-droplets at atmosphere pressure [13]. ESI brought about the ability to provide mass spectrometers with intact molecules that can be ionised in solution of polar solvents (e.g. methanol and water) from where they are directly generated to the gas phase. The ions that can be generated via ESI are typically intact protonated $[M+H]^+$ or deprotonated $[M+H]^+$ molecules or ion/molecule adducts, such as $[M+Na]^+$, $[M+K]^+$ or $[M+Cl]^-$. ESI is most commonly associated with the analysis of large biomolecules of medium to high polarity, and it is a major tool for proteomic analyses [17], but it can also be used for the MS analysis of small molecules provided they contain basic groups (e.g., amino, amide) for positive ESI or acidic groups (e.g., carboxylic acid, hydroxyl) for negative ESI.

The multiple charging feature of ESI permits analysis of high molecular weight ions on low-mass range analysers. Higher MS/MS CID fragmentation efficiently can be obtained for multi-charged ion than for singly-charged ions. The multi-charging phenomenon means that ions of very large mass can be detected with conventional analysers with mass ranges up to 3000 u. Multi-protonated species or multi-charging (e.g. from peptides) can be generated using ESI; this leads to the formation of low *m/z* ions from high mass species, and is the most important outcomes from the invention of ESI.

Despite the exceptional features of ESI (i.e. multi-charging, soft ionization), it does have some noteworthy limitations. The spray nature of ESI means that a sample is constantly being consumed. Unfortunately, however, no mass spectrometer constantly analyses ions, which means that some of the sample is wasted. This can be solved by using mass analysers that have an inherently higher duty cycle and by

developing pulsed ESI sources. The second limitation of ESI is its vulnerability to ion suppression effects. This is due to the high salt concentrations (i.e. > ~1 mM), in most biological samples. For this reason biological samples need to be desalted before analysis. In addition, when analysing analyte(s) in complex mixtures, the higher-concentration of analyte(s) can suppress ion formation by lower-concentration analyte(s).

Atmospheric pressure chemical ionisation (APCI) is another soft ionisation method similar to ESI. The ionisation process in APCI occurs at atmospheric pressure through ion/molecule reactions. In APCI ion generation from a sample is accomplished by a corona discharge generated from a sharp needle. Approximately, 1- 5 kV is applied to the needle to generate a corona discharge. Electrons from this corona discharge ionise reagent molecules such as N_2, O_2, H_2O and NH_4 (solvent molecules) that are in direct proximity of the sharp needle. Both positive and negative ions are formed due to either protonation, which generates positive ions, or deprotonation, which gives negative ions. Like ESI, APCI has several notable features.

APCI can be readily coupled to separation techniques (e.g., HPLC) like ESI. In contrast to ESI, APCI has the advantage of being less susceptible to matrix ion suppressions from salts. APCI also has the advantage over ESI in that weakly polar analyte(s), not existing as preformed ions in solution, can be readily ionised; this makes APCI and ESI complementary ionisation methods. The reduced matrix susceptibility and ability to ionise weakly polar analyte(s) often makes APCI suitable for drugs and human metabolites profiling with very high sensitivity despite its compatibility with a wide range of analyte(s), APCI has some shortcomings. For

instance, thermally labile compounds can decompose in the heated carrier gas (150-300^{o}C).

Matrix-assisted laser desorption/ionisation (MALDI) is another soft desorption atmospheric ionisation method. Unlike ESI in which ions are sprayed continuously, in MALDI ions are produced by irradiating a pulsed laser to a solid analyte(s). The analyte(s) is co-crystallized with a solid matrix that absorbs light energy emitted from a laser, ablating the surface and forming a plume containing gas-phase matrix and analyte(s) ions. The process of generating ions using MALDI is always performed in the vacuum; however, recently, it has been shown that ion generation using MALDI can be done at atmospheric pressure. In MALDI singly-protonated analyte(s) are always obtained. However, the mechanism by which ions are formed is not fully clear which warrants investigation. Nevertheless, MALDI has several advantages.

In MALDI ions are formed in discrete events due to the pulsed nature of most lasers used, and if mass analysis can be synchronized with ion formation, very little sample is wasted. High sensitivity and specificity can be achieved with a small amounts of the samples (sub-femtomole ($< 1 \times 10^{-15}$ moles)) using MALDI. Furthermore, MALDI has higher salt and buffer tolerance compared to ESI; hence ions can be formed by MALDI from samples that contain higher levels of salts.

Despite the significant advantages discussed above MALDI has some shortcomings. Even though the pulsed nature of the method is one source of MALDI's inherent sensitivity, it is also a source of difficulty when coupling to some mass analysers. Consequently, only certain mass spectrometers are easily coupled with MALDI. Also, the presence of a matrix, which facilitates ionisation, causes a large degree of chemical noise to be observed at *m/z* ratios below 500 Th. As a

result, samples with low molecular weights are usually difficult to analyse by MALDI. Other desorption ionisation methods such as photo ionisation allow a narrow ionisation energy band to be selected and as such are uniquely suited for controlled fragmentation [16].

Photo ionisation is independent of surrounding molecules and involves photon absorption followed by ejection of an electron. Consequently probing of state-selected molecular fragmentation dynamics can be achieved by coincidence measurements of several particles [17, 18]. This has led to ultrafast molecular dissociation mechanisms being proposed [19, 20]. Synchrotron radiation based photo ionisation is also used as a soft activation technique for MS/MS [21] and as a means of studying the inner-shell spectroscopy of gas-phase proteins [22]

When an atmospheric ion source (e.g. ESI/MALDI/APCI) is used in MS analysis, analyte(s) molecules that can readily attach a hydrogen ion (H^+) in the gas phase will be ionised via proton transfer reaction to form protonated $[M+H]^+$ molecular ion species in the positive ion mode. While those that can readily lose H^- will be ionised via hydride subtraction to form $[M-H]^+$ molecular species in the negative ion mode. Protonation is the addition of one or more protons to a compound so that the net charge of the compound is positive. While deprotonating/hydride abstraction is the removal of one or more protons from a compound so that the net charge of the compound is negative.

Alternatively adduct anions such as chloride $[M-Cl]^-$, or cations; sodium $[M+Na]^+$ and potassium $[M+K]^+$ can be formed the negative and respectively [23]. The formed gas phase ions at atmospheric pressure are transported to the mass spectrometer through the atmospheric pressure interface. The transport mechanisms for this action can include: (i) static charge accumulation on the insulating surface,

(ii) momentum transfer in the case of gaseous ion/charge micro-droplet impact on the molecular species on the surface, and (iii) the suction of the vacuum at the inlet of the transfer capillary. However, ionising a sample using these soft ion sources require sample introduction systems that almost prohibit direct sampling of samples in their native environments.

Today, molecular ionisation methods have matured to the point where it is possible to record mass spectra on samples in their native state with little or no sample preparation, referred to as ambient ionisation mass spectrometry (AI-MS) [24]. Ambient ionisation (AI) methods based on either ESI or APCI and a variety of other related ionisation techniques (Table 1.3), are therefore moving MS forward in applications where they are increasingly deployed for *in-situ* chemical analysis [25]. AI-MS offers the direct analysis of untreated samples without the need of tedious sample preparation procedures (e.g. extraction or derivatisation). The shortcomings of sample contamination or alterations, that might bring doubts to the sample integrity are therefore minimised.

The concept of ambient ionisation and sampling prior to mass spectrometric analysis was first introduced in 2004 by Prof Cooks at Purdue University with the invention of desorption electrospray ionisation (DESI) [26]. Since then more than 50 AI ionisation sources have been introduced to the scientific community (see Table 1.3 for details). This new trend of performing both qualitative and quantitative mass spectrometric analysis is centred on the idea of direct *in-situ* MS analysis on unprocessed samples in their natural environment. Such samples could be bricks, bodily fluid (e.g., blood, urine), clothing, biological tissue, etc. DESI is an AI method spray-based technique that combines all the attributes of ESI with the additional benefits of direct surface desorption and ionisation of analyte(s) from

different surfaces [27]. In DESI, a fine nebulized electrospray of high velocity charged liquid micro-droplets of polarity (+v or –v) are used to bombard a sample deposited at a surface, causing desorption (droplet pick up) of a sample and its ionisation in concert. The ionised sample is then transported to the mass spectrometer in secondary micro-droplets through a transfer capillary (Figure 1.2, upper).

In parallel with the development of DESI another ambient ionisation source, direct analysis in real time (DART) [28] was introduced. DART is a solvent-free AI method performed normally on a heated helium gas stream which combines several ionisation mechanisms. Ionisation is promoted by glow discharge that produces electronically excited He* metastable, forming a series of ion such as H_3O^+ and O_2^-. Subsequently via atmospheric pressure chemical ionisation (APCI), the analyte(s) ions are generated. In DART an electrical potential is applied to a gas with a high ionisation potential (e.g., Nitrogen or Helium) to form a plasma of excited-state atoms and ions, and these desorb low molecular weight molecules (Figure 1.2, lower). The advance represented by AI methods, addresses the practical aspect of laborious sample preparation prior to MS analysis.

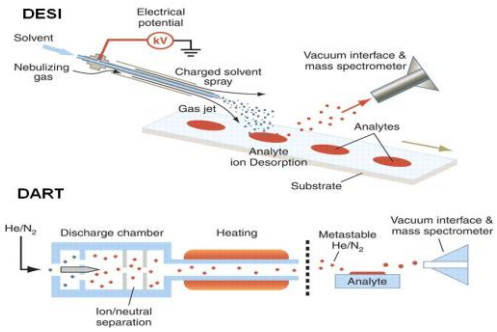

Figure 1.2: DESI (upper) and DART (lower) ionisation for ambient high-throughput mass spectrometric analysis of unprepared samples (e.g. skin, bricks, urine, clothing, tissue, etc.). Reproduced from reference [24] with permission.

No.	Ambient Ionisation Method	Acronym	Agent
1	Desorption electrospray ionisation [26]	DESI	Charged micro-droplets
2	Easy ambient sonic-spray ionisation [29]	EASI	Charge micro-droplets
3	Desorption ionisation by charge exchange [30]	DICE	Charge micro-droplets, CI
5	Transmission mode desorption electrospray ionisation [31]	TM-DESI	Charge micro-droplets
6	Nonospray-desorption/electrospray ionisation [32]	noDESI	Charged micro-droplets
7	Probe electrospray ionisation[33]	PESI	Charged micro-droplets
8	Liquid micro junction-surface sampling probe [34]	LMJ-SSP	Charged micro-droplets
9	Paper spray [35]	PS	Charged micro-droplets
10	Direct analysis in real-time [28]	DART	Plasma
11	Low-temperature plasma probe [36]	LTP	“
12	Flowing atmospheric pressure afterglow [37]	FAPA	“
13	Desorption atmospheric pressure chemical ionisation [38]	DAPCI	“
14	Desorption corona beam ionisation [39]	DCBI	“
15	Dielectric barrier discharge ionisation [40]	DBDI	“
16	Electrospray-assisted laser desorption ionisation [41]	ELDI	Photons, Charged micro-droplets
17	Laser ablation electrospray ionisation [42]	LAESI	“
18	Laser-assisted desorption electrospray ionisation [43]	LADESI	“
19	Laser desorption electrospray ionisation [44]	LDESI	“
20	Laser-induced acoustic desorption-electrospray ionisation [45]	LIAD-ESI	Photons, Charged micro-droplets
21	Neutral desorption extractive electrospray ionisation [46]	ND-EESI	Charge micro-droplets
22	Radio-frequency acoustic desorption and ionisation [47]	RADIO	Charged micro-droplets
23	Atmospheric pressure solids analysis probe [48]	ASAP	Heat , Plasma
24	Infrared laser ablation metastable-induced chemical ionisation [49]	IR-LAMICI	Photons, CI
25	Rapid evaporative ionisation mass spectrometry [50]	REIMS	CI
26	Desorption atmospheric pressure photo-ionisation [51]	DAPPI	CI
27	Beta electron-assisted direct chemical ionisation [52]	BADCI	CI
28	Extractive electrospray ionisation [53]	EESI	Charged micro-droplets
29	Remote analyte sampling transport and ionisation relay [54]	RASTIR	“
30	Laser ablation flowing atmospheric-pressure afterglow [55]	LA-FAPA	Plasma
31	Surface activated chemical ionisation [56]	SACI	“
32	Single particle aerosol mass spectrometry [57]	SPAMS	Photons
33	Laser diode thermal desorption [58]	LDTD	Photons, Plasma
34	Helium atmospheric pressure glow discharge ionisation [59]	HAPGDI	“
35	Surface acoustic wave nebulization [60]	SAWN	Acoustic
36	Ultrasonication-assisted spray ionisation [61]	UASI	“
37	Atmospheric pressure-thermal desorption/electrospray ionisation [62]	AP-TD/ESI	Heat, Charged micro-droplets,
38	Microplasma discharge ionisation [63]	microsplama	Plasma
39	Desorption electrospray/metastable-induced ionisation [64]	DEMI	Charged micro-droplets, Plasma
40	Switched ferroelectric plasma ioniser [65]	SwiFerr	Plasma
41	Ambient Surface-Assisted Laser Desorption/Ionisation [66]	Ambient SALDI	Photons, Plasma
42	Plasma-assisted desorption ionisation [67]	PADI	Plasma
43	Desorption electro-flow focusing ionisation [68]	DEFFI	Charged micro-droplets
44	Touch Spray Ionisation [69]	TSI	Charge micro-droplets
45	Electrospray-assisted laser desorption Ionisation [70]	ELDI	Charged micro-droplets, Photons

Chemical ionisation (CI) agents: Ionised solvent species obtained after heating, or bombardment of solvent molecules with highly energetic photons or electrons act as proton source.

Table 1.3: List of ambient ionisation methods, acronyms, agents, characteristics and references.

1.2. Laying the Mass Spectrometry Foundations

MS in its modern form has been the consequence of important scientific and technological advances in the past. In particular, developments in the 19th century which elucidated the electrical nature of matter and later the application of Newtonian mechanics to the motion of electrical charges (electrodynamics). Both were significant in laying the foundations of MS. Historically, ideas on the atomic nature of matter can be traced back to the ancient Greeks. However such ideas were to lay dormant for nearly 2000 years until the 19th century through the work of scientists like Dalton (laws of chemical combination), Maxwell (kinetic theory of gases) and Faraday (ions in electrolysis) to name but a few [71].

The first stage of MS is to generate gas phase ions. The term "ion" (along with the terms "anion" and "cation") was first introduced by Faraday in 1834 [72]. He used it to describe the charge carriers which passed between electrodes immersed in an aqueous medium. In 1870 the English physicist Crookes invented the 'Crookes tube', an electrical discharge tube developed from the earlier 'Geissler tube'. The key advance made by Crookes was to use an improved Sprengel vacuum pump [73]. The reduced tube pressure meant an increased mean free path for the negatively charged particles making up the cathode ray beams. An early observer of charged particles was the German scientist Goldstein who advanced the understanding of glow discharge tubes naming the observable light emissions (from the Crookes tube) as cathode rays [74]. In 1886 he discovered what he termed 'canal rays' while studying the electrical discharges observed when the cathode of a cathode-ray tube was perforated [75]. He observed that canal rays travelled in the opposite direction to the (then unidentified) negatively charged particles of cathode rays and therefore must be positively charged (Figure 1.3).

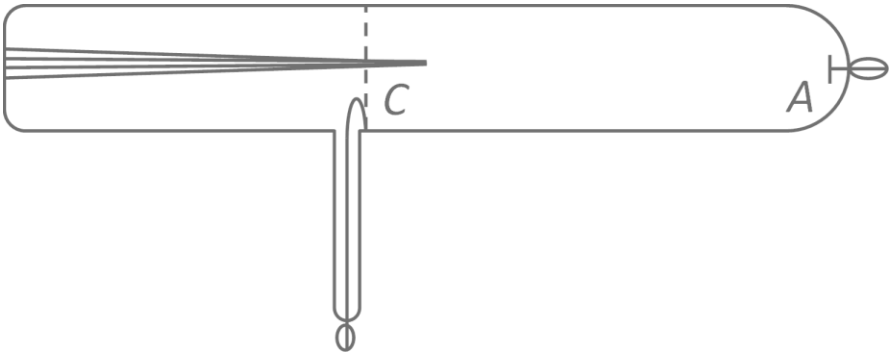

Figure 1.3: Canal rays formed in front of the perforated cathode (C) in a discharge tube. A is the anode. Adapted from reference [76] with permission.

In 1895 the French physicist Perrin confirmed that canal rays were positively charged and that the charge magnitude was approximately equal to that of the cathode rays [77]. This discovery prepared the way for the historic experiments of Thomson in 1897 [78] leading to the discovery of the electron (originally termed "corpuscles") which led to him receiving the Nobel Prize in Physics (1906).

Thomson confirmed that cathode rays consist of negatively charged particles and was able to measure the ratio of the electric charge of a particle to its mass (*e/m*). Using a similar experimental approach to Perrin, Thomson deflected the cathode rays with a magnet to determine if the charge and rays could be separated. He found that they could not and concluded that they are the same thing. This was confirmed by deflecting the cathode rays with a magnet away from the detector for which no appreciable signal was observed. However when the cathode rays were deflected towards the detector the signal increased. In his second experiment, Thomson attempted to deflect the cathode rays by applying an electric field between a pair of metal plates, an experiment previously carried out by Hertz [79]. Thomson was able to observe the beam deflection produced by the electrically charged metal plates (Figure 1.4). Hertz had previously observed no effect. This was possibly due to poor vacuum conditions and/or space charge effects on (or near) the sides of the tube

shielding the externally applied field. In the third of Thomson's historic experiments he used a combination of electric and magnetic fields and was able to infer the ratio *e/m* of the corpuscles.

By adjusting the magnetic field strength in the region between the metal plates Thomson was able to cancel the deflection essentially balancing the forces due to the electric and magnetic fields. Using the force law proposed by Lorentz [80] which combines the force contributions from the electric and magnetic fields, Thomson was able to deduce the mean velocity of the particles. Thomson then proceeded to measure the deflection of the cathode rays due to the electric field alone; knowing the length, separation and applied voltage across the metal plates as well as the horizontal speed of the rays, the charge-to-mass ratio (*e/m*) was calculated using equation (1),

$$\tan\theta = \left(\frac{e}{m}\right)\frac{Vl}{dv_x^2}. \qquad (1)$$

Here, V is the voltage applied to the plates, l is the length of the plates, d is the plate separation, v_x is the horizontal velocity of the cathode rays, and θ is the angle of the beam deflection.

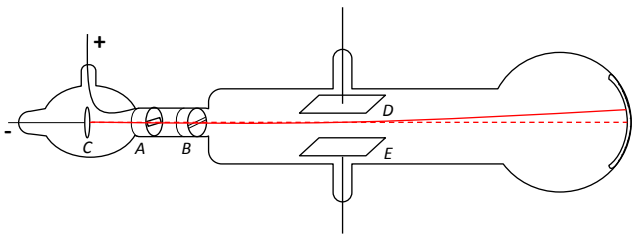

Figure 1.4: Schematic of Thomson's cathode ray deflection apparatus. Rays from the cathode (*C*) pass through a slit in the anode (*A*) and through a slit in a grounded metal plug (*B*). A voltage is applied between aluminium plates (*D* and *E*) and a scale situated on the end of the tube measures the ray deflection. Adapted from reference [78] with permission.

Thomson had discovered the essential nature of the cathode rays; however, the nature of canal rays remained to be identified. The magnetic and electric deflection of canal rays was first measured by Wilhelm Wien in 1898. He found that the velocity of canal rays was much smaller than that of the cathode rays and that the corresponding ratio *e/m* was also smaller. In his experiments, Wien identified an unknown positive particle (which we now know as a proton) to be equal in mass to the hydrogen atom [81]. Wien also received a Nobel Prize in physics (1911) but for his earlier work regarding thermal radiation. Thomson, in considering the work of Wien with canal rays (positive rays), commented:

"The composition of these positive rays [investigated by W. Wien] is much more complex than that of the cathode rays, for whereas the particles in the cathode rays are all of the same kind, there are in the positive rays many different kinds of particles. We can, however, by the following method sort these particles out…" [82]

Thomson began working with positive rays in 1899 following his interest in the experiments of Wien [83]. By 1911, using a refined version of Wien's experimental setup, which included improved vacuum conditions and a photographic plate method of detection, Thomson was able to distinguish different "electric atomic weights" (the ratio of *m/e* for a compound compared to hydrogen *m/e*) [84]. The magnetic and electric fields were oriented so as to produce orthogonal deflections such that a parabolic curve was recorded on the photographic plate for identical species of varying speed. The lines recorded represented the different electric atomic weights of the residual gases in the chamber which had been ionised and deflected accordingly on the photographic plate.

1.3. The Birth of Mass Spectrometry

In 1912, Thomson invented the world's first scanning mass spectrometer, which he called a "parabola spectrograph" [85]. In doing so, he first had to refine his detection method in order to measure relative abundance. He removed the photographic plate and instead made a parabolic slit in a metal plate. Behind the slit he placed a Faraday cup connected to an electroscope. By adjusting the magnetic field, each positive ion beam could be deflected through the slit and the intensity measured. Thomson could then plot a mass spectrum of ion abundance against relative mass. Mass spectrometry was born.

Ion detection methods had shifted from fluorescent tubes [86, 87] to photographic plates [88] and then ion collectors (Faraday cup). The difference is subtle yet significant. Photographic plates (and fluorescent tubes) provided a visible trace of all the various ions i.e., simultaneous detection of all the *e/m* species present were recorded at any given time. However, these detection methods were only capable of providing a qualitative and at best semi-quantitative measurement; the net result being an image spectrum. Whereas incorporating ion counting detection methods and causing only a single *e/m* to be recorded for a given set of conditions, Thomson was able to measure ion intensity and produce a mass spectrum (Figure 1.5) [89].

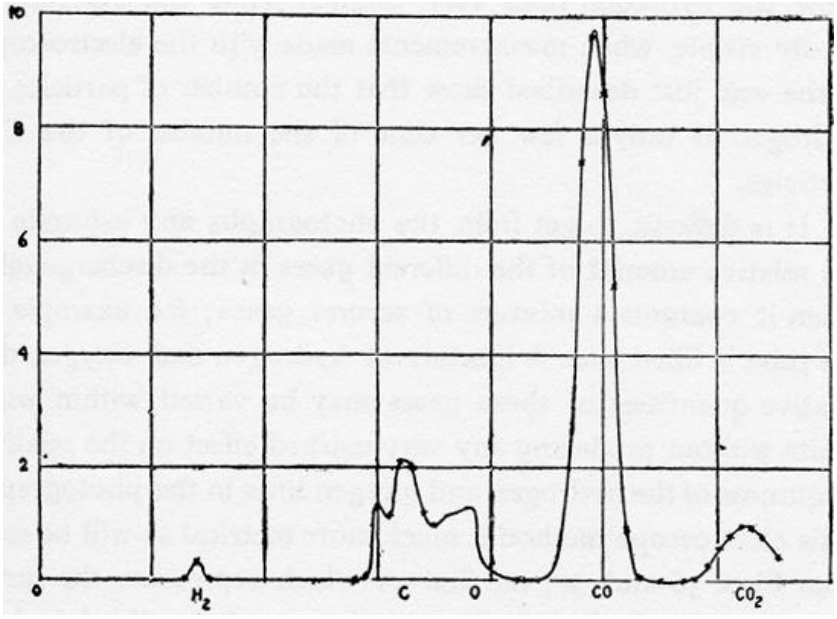

Figure 1.5: Thomson's mass spectrum of carbon monoxide (CO). Reproduced from reference [89] with permission.

In 1913, Thomson published a monograph entitled "Rays of Positive Electricity and Their Application to Chemical Analysis" [89]. The foresight of Thomson regarding the potential of this analytical technique was evident in the foreword: *"... one of the main reasons for writing this book was the hope that it might induce others, and especially chemists, to try this method of analysis. I feel sure that there are many problems in Chemistry which could be solved with far greater ease by this than by any other method."*

At the same time Thomson demonstrated the application of positive rays (canal rays) for chemical analysis using inert gases. He observed that the main ray of Neon (Ne) at *m/e* 20 was accompanied by a weaker signal corresponding to *m/e* 22; in addition, he found *m/e* 10 and 11, equivalent to doubly charged ion species (Figure 1.6). At first Thomson was cautious in the interpretation of his results and instead left the topic open ruling out several of his own suggestions (such as doubly charged carbon dioxide, neon hydride and a new element).

He concluded,

"… neon is not a simple gas but a mixture of two gases, one of which has an atomic weight about 20 and the other about 22" [89].

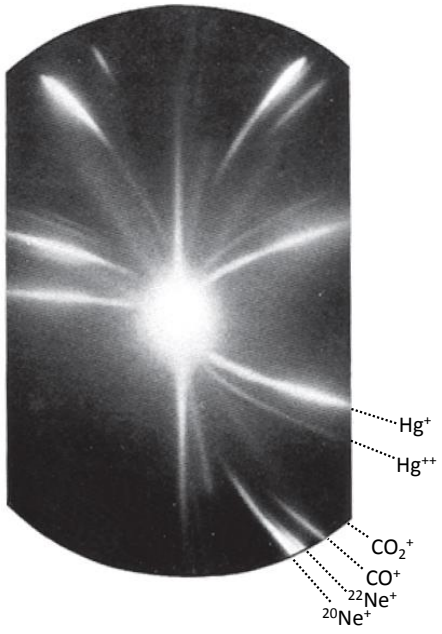

Figure 1.6: Parabola Spectrograph result showing isotopes of ^{20}Ne and ^{22}Ne. Adapted from reference [87] with permission.

1.3.1. Discovery of Isotopes

Following the end of the First World War, Aston, previously a research assistant to Thomson but now under the direction of Rutherford, tried to understand the mystery of the *m/e* 22 line in the image spectrum of Neon. In doing so he re-defined the concept of isotopes to include stable and not just radioactive elements. At first Aston tried methods such as fractional diffusion and density measurements but with no success [90]. When these methods failed, Aston returned to mass spectrometry. He constructed a new "mass spectrograph" [90, 91] superior to the parabola spectrograph of Thomson with 10 times the resolving power. Aston's

spectrograph used successive electric and magnetic fields to bring about velocity focusing such that ions could be collimated independent of their velocity [90]. The mass spectrograph formed the basis of Aston's later designs which he used to identify 212 naturally occurring isotopes. Aston received the Nobel Prize in Chemistry (1922) for his discovery of isotopes (by means of his mass spectrograph) and for his enunciation of the whole-number rule [92].

1.3.2. Single Focusing Magnetic Sector

Around the same time in 1918, Dempster at the University of Chicago constructed a magnetic sector analyser and laid the ground work for electron impact ionisation [93]. Using his magnetic sector analyser, Dempster reported the discovery of several isotopes including three isotopes of magnesium [93], four isotopes of zinc, and is credited with the discovery of Uranium 235 [94].

Dempster's magnetic sector analyser established the basic design theory that is still used for sector instruments today (Figure 1.7). In Dempster's instrument ions are accelerated from the ion source (G) through a narrow slit (S_1). They are then deflected through 180° by a homogenous magnetic field in the analyser region (A) and ions of a particular *m/z* are allowed to pass through a second slit (S_2) and register a charge on the electrometer (E).

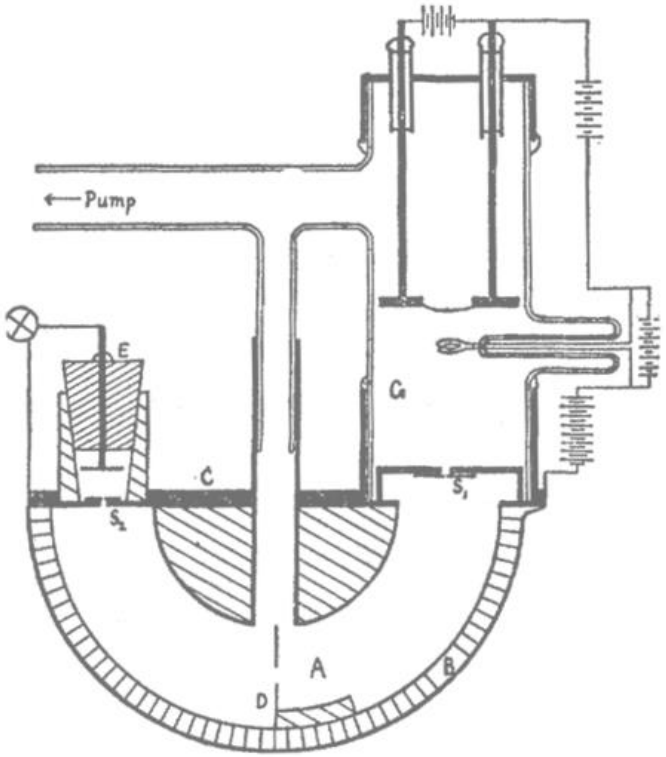

Figure 1.7: Dempster's 180° magnetic sector instrument. Reproduced reference from with permission [93].

Magnetic sector instruments separate ions in a magnetic field according to their charge and momentum. The principle of operation is based on the Lorentz force and the angular momentum of the ion. The trajectory of an ion follows a circular path as it passes through the magnetic field region. Ions of a specific *m*/*z* will have a unique radius (*r*) of curvature (for constant velocity (*v*) and magnetic field (*B*)) as given by equation (2),

$$\frac{m}{z} = \frac{Ber}{v}. \qquad (2)$$

1.4. Development of Mass Spectrometry

In 1929, Bleakney improved on the work of Dempster through the development of the electron impact ion source [95]. This is now used as a standard ionisation source in MS. In electron impact ionisation (also known as electron ionisation (EI), energetic electrons produced by thermionic emission interact with gas phase neutrals to produce ions. The improvement made by Bleakney was to separate the fields controlling the electron and ion beams thus providing improved measurements of molecular ionisation. Furthermore, the resulting mass spectrum would include a fragmentation pattern which could be considered as a “finger print” for characterizing a sample. Further progress with EI sources was made by several researchers in the 1930s including Mattauch [96-99]. Such advances led to the use of MS in the study of complex molecular structures, such as hydrocarbons [100].

The resolution of the 180° magnetic sector instrument developed by Dempster, was hampered by large spread in velocity of the mass-to-charge ions entering the analyser. Dempster realised this and proposed a so-called "double focusing" design which included velocity as well as directional focusing [101]. The basis of the velocity filter (also known as a Wien filter) was previously developed by Wien [81] in his investigations of canal rays. This had been employed in Aston’s Mass Spectrograph which consisted of electric and magnetic fields perpendicular to each other creating a velocity spectrum and permitting only a narrow band of ion velocities to be transmitted.

Further improvements in technology and understanding of the sector instrument led to the development of the double focusing sector instrument. This instrument incorporates both direction and velocity focusing in order to refocus ions using a magnetic and electric sector. The double focusing instrument is able to obtain

higher resolution and sensitivity than a single focusing instrument with a velocity filter. this is because it refocuses ion beams that are inhomogeneous in both velocity and direction without loss of signal. The first double focusing instrument was described by Mattauch and Herzog in 1934 [88]. Similar instruments were developed in the 1930s by Dempster (Dempster, 1935) and Bainbridge & Jordan [102]. Nier & Johnson [97, 103] developed an arrangement which was particularly successful in reducing second order angular aberrations (i.e., improving second order direction focusing) permitting a larger angular spread of ions leaving the ion source [103]. Their design used a 90° electrostatic analyser followed by a 60° magnetic sector field, minimising the interference of the electromagnet with the ion source and detector.

Up until the early 1950s the majority of mass spectrometers (or spectrographs) which had been developed relied on magnetic fields for mass analysis. These instruments are commonly referred to as ‘static’. Static instruments have electric and/or magnetic fields that remain constant during the passage of an ion, exemplified by the mass spectrograph which records various *m/e* ion beams at different locations on a photographic plate. In contrast a dynamic instrument uses time varying fields to focus ions of a given *m/z* on to a suitable detector and therefore allowing rapid identification of a wide range of constituent components from a sample.

In 1946, Stephens described a new concept for dynamic MS using time dispersion [104], which became known as Time-of-Flight (TOF) MS. A TOF MS uses differences in ion transit time through a drift region (free of electric field) to separate ions of different masses. It operates on the principle that ions of the same kinetic energy but different masses take different time intervals to traverse a fixed

distance. The ions are accelerated by an electric potential (U). The flight times of ions are measured with respect to the start of an extraction pulse. The flight time (t) required to traverse the length (l) of the drift region, assuming constant ion kinetic energy, is proportional to the square-root of the mass-to-charge ratio and is given by equation (3),

$$t = \frac{l}{\sqrt{2Ue}}\sqrt{\frac{m}{z}}\,. \qquad (3)$$

The end of the 1940s saw the development of a new technique used for surface science analysis, namely secondary ion mass spectrometry (SIMS). It had long been known that the bombardment of a solid sample surface with a focused primary ion beam caused the emission of secondary ions characteristic of the sample. SIMS is a technique which collects and analyses the desorbed (secondary) ions. The process was first noted by Thomson in 1910 [84]. With the aid of improved vacuum technology, Herzog and Viehböck performed the first SIMS experiments in 1949 [105]. The benefits of this technique for surface analysis have opened up a number of application areas for example in the analysis of moon rock conducted by NASA [106].

In 1949 a further step towards high resolution MS was made by Hipple and co-workers who described Ion Cyclotron Resonance (ICR) MS [107, 108]. Their initial aim was to determine the Faraday constant by measuring the cyclotron resonance frequency of protons. The basis of their development was the pioneering work of Lawrence and Livingston who developed the cyclotron in the early 1930s [109] accelerating protons at high speed for nuclear physics experiments. The basic

mass separation principle of ICR MS relates to the ion cyclotron resonance frequency (*f*) of each ion as it rotates in the magnetic field (*B*). A spectrum is obtained by scanning the magnetic field of an electromagnet to bring ions of different *m*/*z* to resonate based on the equation (4),

$$\frac{m}{z} = \frac{eB}{2\pi f}. \qquad (4)$$

A notable milestone in the quest for high performance MS was met in the early 1970s by the development of Fourier transform ion cyclotron resonance (FTICR) MS by Marshall and Comisarow [110]. The essential principles of this technique are derived from conventional ICR MS [111] and the use of FT in nuclear magnetic resonance (NMR) [131]. In FTICR MS, sample ions are held in a Penning trap [112] where they are excited by an oscillating electric field until they are separated out according to their *m/z* value, rotating in phase at their cyclotron frequencies. The ion signal is detected as an image current and the resulting signal is converted from the frequency domain by applying Fourier transform to give a mass spectrum.

In 1953, a new concept in mass analysis, the Quadrupole Mass Spectrometer (QMS), was first described by Paul and Steinwedel [113]. They specified a new type of dynamic mass analyser which separates ions based on their stability within a quadrupolar field, using a combination of sinusoidal (*V*) and static (*U*) voltage potentials. A simple quadrupole mass analyser consists of four parallel electrodes, with hyperbolic cross-section, accurately positioned in a radial arrangement such that they are equally spaced about a central axis, extending in the *z* direction (direction of the ion beam).

The methods of scanning and motion of an ion in an ideal quadrupole based analysers is described by the Mathieu equation (5),

$$\frac{d^2u}{d\xi^2} + \left(a_u - 2q_u \cos 2\xi\right)u = 0. \qquad (5)$$

where u is displacement (x, y), ξ is a dimensionless time parameter given by, $\xi = \frac{\omega t}{2}$, ω is the angular frequency of the sinusoidal voltage, r_0 is the inscribed radius of the quadrupole or trap electrode set and a_u & q_u are dimensionless stability parameters given by equation (6) and (7),

$$a_x = -a_y = \frac{8eU}{m\omega^2 r_0^2}, \qquad (6)$$

$$q_x = -q_y = \frac{4eV}{m\omega^2 r_0^2}. \qquad (7)$$

where x is the respective dimension (x, y, r, *or* z), e is the unit elementary charge, U is the amplitude of the DC potential applied between the rods, V is the amplitude of the radio frequency (RF) potential applied to the rods, m is the mass of the ion.

The four experimental parameters that determine the stability of an ion in a quadrupolar field are thus (i) the amplitude of the DC potential, (ii) the frequency of the applied fundamental RF waveform, (iii) the radius of the device, and (iv) the RF amplitude. In a quadrupole mass filter, ions are selected for detection by mass selective stability, wherein the amplitudes of the RF and DC are increased while either keeping their ratio constant or changing their ratio slightly to increase resolution with mass and maintain unit resolution. This way, ions of consecutive

masses are successfully brought to the apex of Mathew stability diagram [113], causing all other ions to become unstable. If the ramp of the RF and DC components is linear, time domain current or voltage data are linearly related to *m/e* (i.e. m/e is directly proportional to the *V*/*U* amplitude.

In the original work of Paul and co-workers, much emphasis was placed on the fact that the QMS separates ions without the use of magnetic fields. Recent investigations have shown that applying a magnetic field to the body of the QMS electrode assembly can enhance device performance [114,115].

An adaptation of the QMS was proposed in 1963 by Von Zahn, a co-worker of Paul, who invented the monopole [116]. The monopole geometry consists of one circular electrode and an angled v-shaped electrode producing one quarter of the QMS field. Initially this instrument was met with much interest until it was realized that this device was inferior to the QMS due to the poor peak shape and low sensitivity. It is worth noting that a relatively recent report by Sheretov *et al*. [117] has shown, the use of hyperbolic geometry for both electrodes, improves resolution fourfold and sensitivity one hundred fold over the conventional monopole design.

The QMS became a very popular instrument among analysts due to its suitability for coupling with gas chromatography (GC). The combination of these two methods GC and MS provides a powerful means for identification of substances within a test sample and is often referred to as the "Gold standard" for forensic substance analysis. The role of GC is to initially separate mixtures (in time) into their components; the mass spectrometer then acts as detector for identifying and quantifying each component [118]. The original investigator of this combination of techniques was Beynon [119]. The QMS is the prime mass spectrometer for coupling with GC due to its fast scanning speeds. Relatively low mass range compounds are

typically investigated (< ~500 *m*/*z*), where the need for high resolution spectra is not normally required.

Paul and Steinwedel filed patents in several countries for the QMS [120, 121] and the quadrupole ion trap (QIT) mass analysers also known as a “quadrupole ion stores. The QIT mass analysers use electrostatic fields such as RF, DC and a combination thereof to form and contain ions within a physical structure. In general, a quadrupole electric field provides an ion storage region by the use of a hyperbolic electrode structure or a spherical electrode structure which provides an equivalent quadrupole trapping field. The QIT differs from the QMS in structure by utilising three electrodes. There are two end-cap electrodes which have hyperbolic geometry with one or more holes in the centre and which act as the entrance and exit electrodes. The third electrode is a hyperbolic ring situated centrally between the end-cap electrodes.

The storage of ions in an ion trap is achieved by operating trap electrodes with values of RF. voltage V and associated frequency f, DC voltage U, and device size r_0 and z_0 (trapping parameters) such that ions having mass-to-charge ratios within a finite range are stably trapped inside the device. For stably trapped ions the component of ion motion along the axis of the trap may be described as an oscillation containing innumerable frequency components, the first component (or secular frequency) is the most important and of the lowest frequency, and each higher frequency component contributing less than its predecessor. Although quadrupole ion traps were first used as mass spectrometers, these mass analyser devices did not gain wide use due to the difficult and insufficient mass analysis methods that yielded poor mass resolution and limited mass range [122, 123].

The introduction of the a better method of ion trap operation, the "mass-selective instability mode" provided the first practical method of mass analysis with a QIT and resulted in the wide acceptance and general use of ion trap mass spectrometers for routine chemical analysis [122, 123]. In this mass analysis mode a mass spectrum can be recorded by scanning ions sequentially out of the trap in order of increasing *m/z* (mass/charge ratio, also thomson, Th) by ramping the amplitude of the driving radiofrequency (RF) waveform. The RF ramp causes ion trajectories to become unstable in one or more dimensions as the ions are brought to the working point (e.g., q_z = 0.908) where q_z is the classic Mathieu parameter for the *z* axis (Figure 1.8), and the z instability allows the ions to be detected externally [122,123, 124].

Later, an alternative method of ion trap mass analysis, “resonance ejection” was introduced. Resonance ejection mass analysis technique employs a small supplementary AC signal to enforce a second working point or “hole” on the q axis (more precisely, on an iso-β line) of the Mathieu stability diagram (Figure 1.8). The ions can then be scanned through the operating point and ejected in order of increasing *m/z* as the RF amplitude is increased, which generally results in increased resolution compared with mass-selective instability or boundary ejection [124-131]. Alternatively, in a new method described recently, the “hole” can be scanned through all possible q values by ramping the frequency of the supplementary AC at fixed RF amplitude in what has been termed a “secular frequency scan” [132].

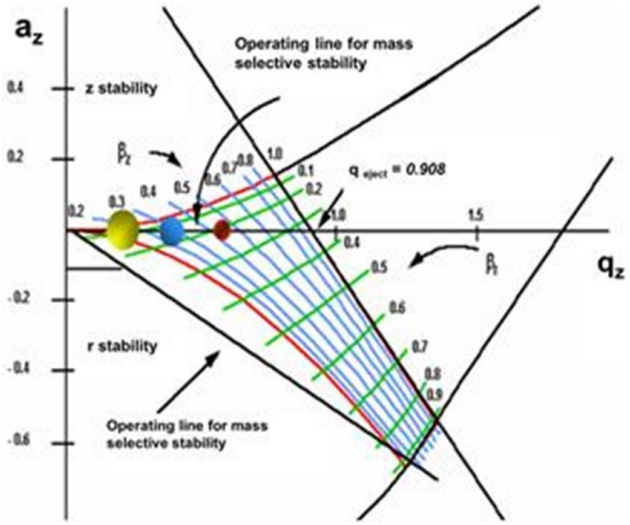

Figure 1.8: Stability diagram for a quadrupole ion trap using *a* and *q* parameters for the coordinate axes. It shows the ion motion stability in the axial (z) dimension in the ion trap, ion motion stability in the radial (r) dimension in the ion trap. Ions that map onto the *a* and *q* coordinates and fall into the stability region are stable in both axial and radial trap dimensions, Reproduced with permission from [140].

When resonance ejection was introduced, the amplitude of the RF potential scanned in a similar way but a supplementary AC voltage with a frequency of only slightly less than one half the RF frequency was applied across the trap's end cap electrodes. Ions were ejected as they crossed the beta line associated with the resonance frequency, a beta value only slightly less than 1. The QIT operates at relatively high pressure (10^{-3} Torr) with a helium buffer gas that assists the ions to maintain stable in the quadrupole field. The buffer gas also serves as the collision gas for collision-induced dissociation (CID) during MS/MS experiments [136].

To perform an MS/MS experiment, a particular ion can be isolated, collisionally fragmented and a scan of all the product ions generated (MS^2 scan). Applying certain voltages on the exit rods ions of a particular *m/z* may be isolated and activated. During CID dissociation the resonance excitation ac voltage is applied to the exit rods. The resonance excitation ac voltage enhances ion motion in the

radial direction and ions gain kinetic energy. After many collisions with helium damping gas the ions gain enough internal energy to cause them to dissociate into product ions. The mass analyzer contains helium (~10-3 Torr) that is used as both, a damping and a collision activation gas. The collisions of the ions entering the mass analyzer with the helium slow the ions so that they can be trapped by the RF field. These collisions reduce the kinetic energy of the ions, thus damping the amplitude of their oscillations. As a result, the ions are focused to the axis of the cavity rather than being allowed to spread through the cavity [134, 135]. Ions may be created inside the QIT or externally using atmospheric pressures ionization methods (Figure 1.9 (b)). From here the ions can be scanned out of the trap using either mass selective instability or resonance ejection method to obtain a full mass spectrum scan of the ions in the trap [120,121, 136].

The MS/MS experiment can be repeated with any one of these fragment ions (MS^3 scan) as long as there are enough ions remaining in the trap to provide an adequate signal-to-noise ratio(S/N), the process can be repeated [131-136].

The QIT is compatible with a wide range of ionizations methods (i.e. ESI, MALDI, CI, APCI, EI etc.) and with all the sample introduction method. The number of ions that can be stored in the QIT or any trapping analyser is limited by the space charge effect. Space charging occurs when the cloud of ions becomes sufficiently dense that coulombic repulsion between the like-charged ions starts to overcome the trapping potential, resulting in degraded mass resolution and accuracy [134-138]. The space charge effect can be minimised by utilising ‘automatic gain control’ (AGC) to limit the number of ions in the trap at any one time. However, this is accomplished at the expense of reduced sensitivity.

Besides the QIT, the linear ion trap (LIT) or 2D trap is another type of mass quadrupolar mass analyser [138]. The LIT mass analysers are based on a four-rod quadrupole divided into three segments in which the short end-segments act as lenses that reflect the ions forwards and backwards in the quadrupole (by the application of appropriate DC potentials), in both the positive and negative modes. The equations of motion for the QIT and the LIT mass analysers are the same. During mass analysis using an LIT analyser all ions are confined in the radial dimension by means of quadrupolar fields and in the axial dimension by means of an electric field at the ends of the trap [139,140]. Considering the position of ions inside the stability diagram (Figure 1.9 a), under certain experimental conditions, if no DC is applied ($U = 0$) and at some RF amplitude V, from equation 6, all ions will possess a_u values of zero, regardless of their mass. Also from equation 7, all ions will have non-zero q_u values, with the heaviest ions having the lowest values and lightest ions having the highest values. As a result ions align themselves along the a_u=0 line of the stability diagram, with the heaviest ions to the left (near q_u= 0), and lighter ions offset to the right due to their different *m/z* values. As with the QIT (see Figure 1.8), if the RF amplitude is now increased, the q-values of the ions will scale proportionally, moving them further to the right of the stability diagram. In the LIT a supplementary AC potential at a frequency corresponding to the secular motion of ions at a selected *q*-value is applied between a pair of opposite electrodes containing slots such that when each of the ions reaches that *q*-value they are ejected radially on to one or other of the two detectors (see Figure 1.9 b)). Typically in a commercial LIT, the selected value of *q* at which ejection of occurs is 0.88 [141].

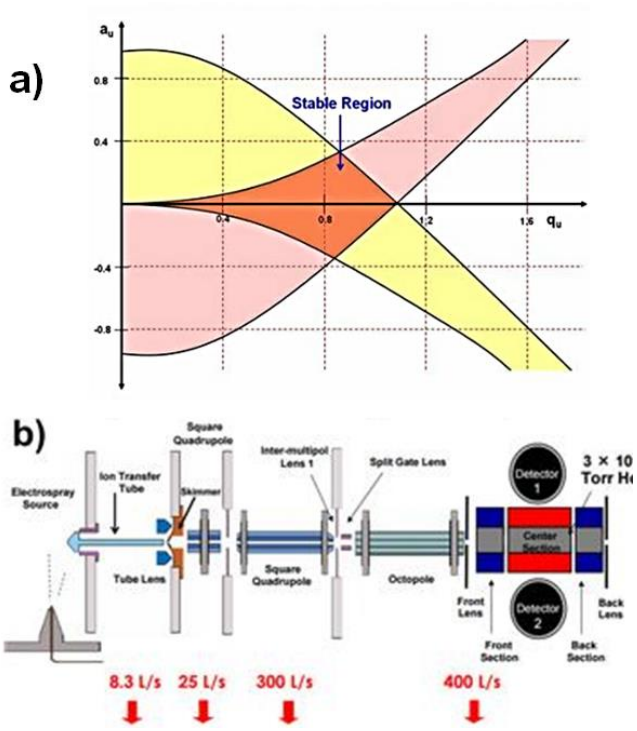

Figure 1.9: The linear quadrupole ion trap (LIT) utilizes an electrostatic potential for confinement of the ion beam. This device has two electrodes placed on either side of a linear space to form the electrostatic potential for the ion confinement. The ion bean is reflected repeatedly between the two electrodes. (a) The stability diagram for the LIT using *a* and *q* parameters for the coordinate axes. (b) Shows a simplified schematic of a commercial LIT (Thermo LTQ) mass spectrometer, with an atmospheric pressure interface. Ions are generated externally by ESI at the extreme left. The generated ions then proceed through the ion transfer tube pass a number of lenses and two RF-multipoles until they reach LTQ ion trap. The generated ions at atmospheric pressure are transported through an RF-only guide/collision quadrupole and then a transport quadrupole to the 2-D ion trap (LIT) which has an internal pressure greater than 3 x 10^{-3} Torr. The LIT has a set of rods (RF and DC) with a ring electrode (DC-only) over the end closest to the exit lens (lens 1). An axial potential well is created in the LIT by biasing the ring electrode. The depth of this well is approximately 1% of the potential difference between the ring electrode and the DC offset of the LIT. Due to collisions with the He buffer gas, ions entering the trap lose sufficient kinetic energy that they accumulate in the well with small axial extent (i.e., a few mm), adapted with permission from [139].

Once the ions enter the LIT, they are cooled by collision with a buffer gas and fly along the *z* axis between the end electrodes while simultaneously oscillating in the *xy* plane owing to the application of an RF voltage on the rods. As a result, the

ions are focused along the axis of the cavity rather than being allowed to spread through the cavity. During ion scan out, the RF voltage is ramped at a constant rate. As the RF voltage increases, ions of increasing *m/z* become successively unstable in the radial direction and are ejected from the mass analyser through slots in the x-pair of electrodes on to externally-mounted detectors [139, 140]. Ejected ions are detected by the ion external detection system [Figure 1.9 (b)).

Also the MS/MS experiment can be performed, when certain voltages are applied on the exit rods, ions of a particular *m/z* may be isolated and activated for MS/MS experiments the same way as in the in the 3-D ion trap. During the MS/MS CID experiment the resonance excitation AC voltage is applied to the exit rods. The resonance excitation AC voltage enhances ion motion in the radial direction and ions gain kinetic energy. As with the QIT, the LIT usually contains a helium gas (~10^{-3} Torr). After many collisions with helium cooling gas the ions gain enough internal energy to cause them to dissociate into product ions.

The LIT has several advantages over the QIT. The larger volume means that more ions can be contained within the LIT before space charging takes effect. This results in a greater dynamic range and improved sensitivity that can translate into lower detection limits for MS/MS analysis. Trapping efficiencies are also increased, as ions entering the trap have to overcome the trapping potential only on the front section. Once the ions are in the trap, the ions are collisionally cooled by interaction with the helium buffer gas and therefore lack the energy to escape the trapping potential on the front and back sections. This is in contrast to the QIT where there is only a narrow time window in which the amplitude and phase of the RF voltage are such that ions can pass through the end cap to enter the trap. However, this limits the trapping efficiency for the QIT to, 1-10% compared to 29 % for the LIT. At different

phases and amplitudes, ions will have either too little or too much momentum so that the ions do not experience a sufficient number of collisions with the QIT buffer gas to be cooled and trapped. Overall the LIT is superior in terms of sensitivity over the QIT [141-146]. In theory the LIT should have the same utility as the QIT in terms of the types of samples and in being interfaced to GC/LC [137]. Paul's pioneering work was recognized by the award of the Nobel Prize in Physics (1989) which he shared with Hans Dehmelt, and Norman Ramsey.

In the early 1970, the triple quadrupole MS was invented by Morrison and developed by Enke and Yost for MS/MS [147]. A triple quadrupole consists of three quadrupoles placed in series but with the central quadrupole acting as a collision cell being operated as an ion guide (see Figure 1.10). MS/MS is particularly useful when analysing complex mixtures. It can be thought of as being analogous to a chromatography/mass spectrometry (for example, LC/MS) experiment in which the first stage of MS separates an individual species from the mixture and the second stage provides the mass spectrum of that species (Figure 1.10). An important advantage of the MS/MS experiment is that either the first stage or second stage of MS can be an independent variable. In the LC/MS experiment, the mass spectrum is dependent on the analyte that is eluting from the column. Therefore, the MS stage is always the dependent variable and the LC stage is always the independent variable.

In MS/MS, however, experiments are possible in which the dependent stage is the first stage of MS (the stage analogous to the LC stage). The experiment most analogous to the LC/MS experiment is called a product ion scan (Figure 1.10 A). In this case, the first stage of MS (MS^1) is the independent stage (that is, fixed parent ion) and the second stage (MS^2) is dependent (that is, scan to detect all the product ions). The goal of the product-ion scan (as well as the LC/MS experiment) is to

identify the selected component of the sample. What is unique to the MS/MS experiment compared with the LC/MS experiment is the ability to screen samples rapidly for certain compound types. One way to do this is for the product ion to be the independent variable (fix MS^2) and the parent ions the dependent variables (scan MS^1 (Figure 1.10 B). This type of experiment is known as a parent-ion (or precursor ion) scan. It is dependent on the analyte parent ions of interest all reacting to give a common product ion. In the product and parent ion scans, the third chemical constituent of MS/MS experiments, the neutral fragment is unimportant. However, in another type of experiment, neutral losses scan (Figure 1.10 C); the neutral fragment is the independent variable. In this experiment, both MS^1 and MS^2 are scanned in such a way that they are offset by the desired neutral mass that is lost (or gained) in the reaction between the two MS stages. Another important type of MS/MS experiment is reaction monitoring (Figure 1.10 D). This experiment is analogous to single ion monitoring in LC/MS, and is typically used for quantification. For a known analyte to be detected, MS^1 is set to pass the parent ion (typically the protonated molecule), and MS^2 is set to pass a known product ion(s). If there is a single parent ion and single product ion, this is a single-reaction-monitoring experiment. There are two forms of multiple-reaction monitoring. In one form, a single parent ion is continually passed through MS^1, and MS^2 is programmed to sequentially pass two (or more) known product ions. This provides added specificity over the single-reaction monitoring experiment, as the parent ion has to dissociate to all the monitored product ions, and the ratio of the product ions should match a known value for the experimental conditions.

An important aspect of the MS/MS experiment is the reaction that occurs between the two MS stages. By far the most frequent reaction is unimolecular

dissociation, which is generally enhanced by some form of ion activation. The ion activation is necessary to increase the internal energy of the parent ion so that it will dissociate before analysis by MS^2. In practice, the activation stage cannot be separated from the dissociation, so the ion activation techniques are typically referred to as dissociation methods. The most common activation/dissociation approach employed in MS/MS is collision induced dissociation (CID) (also known as collisionally activated dissociation). CID is a process wherein a projectile ion is dissociated into smaller fragments as a result of a collision with a target neutral species (typically helium or argon). Other techniques for fragmentation include surface induced dissociation (SID) [148], photon-induced dissociation (PID) [149] and electron capture dissociation [150]. SID involves converting the kinetic energy of an ion to internal energy through a collision with a surface, usually one that has been modified with a self-assembled monolayer [148]. In PID, ions are activated by absorption of a photon(s). Early photo dissociation experiments used UV and visible lasers, typically with beam instruments but generally these are not very efficient experiments [149].

Previously several researchers had investigated ion/molecule collision processes. Significant progress was made independently (and around the same time) by Jennings [151] and by Futrell & Miller [152]. MS/MS can be achieved in *time* (using trap based instruments) or in *space* (with multiple analysers connected in series). A time based approach can perform multiple stages of MS without the need for additional hardware and associated peripherals. The first actual physical arrangement of mass spectrometers in tandem is credited to Lindholm [153]. In MS/MS, for product ion scanning, a pre-cursor ion is first selected by a mass analyser; it is then fragmented typically by CID, followed by mass analysis of the

product ions. The result is a mass spectrum of the fragments of the specified precursor ion providing valuable information regarding the identity and structure of the primary ion (Figure 1.10). The early application of this technique was applied extensively to the study of natural products [154]. Since then MS/MS has become a benchmark procedure for the detailed structural elucidation of complex biomolecules such as proteins [155].

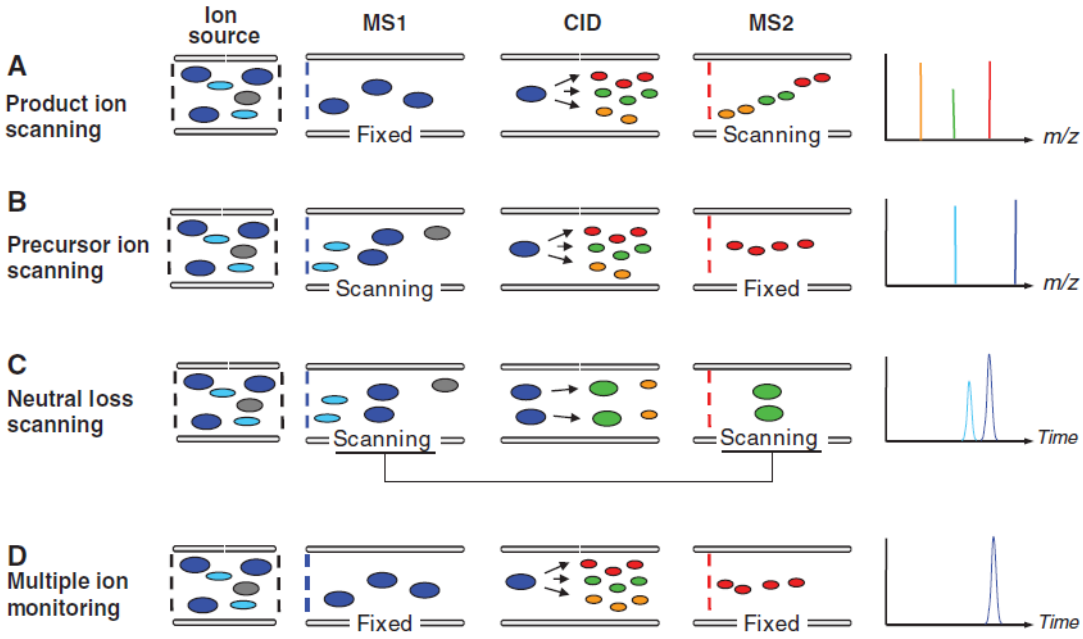

Figure 1.10: This schematic depicts various types of tandem MS experiments using CID: (a) Product ion scanning. In this experiment, the first analyser (MS1) is set to a value that selects one specific precursor ion. The selected ion undergoes CID in the collision cell, and the resulting fragments are analysed by the second analyser (MS2). (b) Precursor ion scanning. This sets the second analyser (MS2) to transmit only one specific fragment ion to the detector. (c) Neutral loss scanning. Both analysers are scanned in a synchronized manner, so that the mass difference of ions passing through MS1 and MS2 remains constant. (d) Multiple Ion Monitoring. This consists of a series of short experiments in which one precursor ion and one specific fragment characteristic for that precursor are selected by MS1 and MS2, respectively. Reproduced from reference [123] with permission.

In 1950-1980 several key developments in ionisation technologies expanding the horizon of MS even further was witnessed. In 1959, H.D. Beckey presented the first focusing field ion source [156,157]. In his early experiments electric field strengths of about 10^8 V cm^{-1} were generated at sharp tungsten tips and used for analysis of bio molecules. The method of field ionisation (FI) was soon extended to the analysis of volatile liquids and solids introduced by evaporation from a sample vial in close proximity to the ionising tip or wire. Further developments to FI led the advent of field desorption (FD) ionisation, because FD circumvents the evaporation of analyte prior to ionisation [162]. Instead, the processes of ionisation and subsequent desorption of the formed ions are cantered on the surface of the emitter.

The specific charm of FI/FD arises from their extraordinary softness of ionisation, in many cases yielding solely intact molecular ions, and from the capability of FD to handle neutral as well as ionic analytes [163]. FI/FD initially flourished from the mid-1970s to the mid-1980s. However, soon suffered from the advent of fast-atom bombardment (FAB) [164] in the early 1980. Ionised species are created when a beam of high energy atoms strikes a surface on which a sample is deposited. The sample is mixed in non-volatile solvent (matrix), and is bombarded under vacuum with a high beam of atoms. The result is continuous desorption of ions allowing substances to be analysed which previously had proved difficult. FAB yield low fragmentation and produces primarily intact protonated molecules denoted as $[M + H]^+$ and deprotonated molecules such as $[M - H]^-$ under a vacuum [165].

Other notable developments during this period included the use of a variety of ion sources thereby extending the range of samples that could be examined and hence the applicability of MS to new fields. Chemical Ionisation (CI) [12] has a similar ionisation process to EI but is a ‘softer’ ionisation method and therefore

enhances the abundance of the molecular ion. The main difference with CI is that the gas pressure in the ionisation source is raised by injecting a reagent gas which increases the probability of forming protonated or deprotonated molecular ions (depending on the reagent gas used).

A significant 'soft' ionisation technique, electrospray ionisation (ESI) was invented in 1968 by Dole [156]. The ESI mechanism is complex but essentially the technique involves an analyte solution being sprayed from a small diameter electrode tip due to an applied high voltage (Figure 1.11). The study of the electrification of liquid (organic solvents) droplets itself has a long history preceding MS. In ESI charged droplets are produced at the capillary tip. The droplets reduce in size due to solvent evaporation and repeated charge-induced droplet disintegrations which lead to small, highly charged droplets. Gas-phase ions are then produced from the droplets. The actual mechanisms for generating gas phase ions differ depending upon the analyte in question [157].

The ionisation of samples in solution for MS was also extended by the use of a membrane interface (known as membrane inlet or membrane introduction - mass spectrometry (MIMS)). MIMS is a technique that allows the direct introduction of specific components of a liquid or gas into the MS vacuum chamber via a semipermeable membrane. It was used in 1963 by Hoch and Kok [158] who originally presented it as a technique for monitoring respiratory gases *in-situ* during photosynthesis. Since then it has been applied to a range of applications such as blood gas analysis [159], fermentation monitoring [160] and underwater environmental profiling [161].

In 1984, the ESI technique originally invented by Dole received considerable development by Fenn et al. who successfully ionised large and fragile biomolecules

for MS analysis [166-168] that can operate under atmospheric presure. Due to the multiply charged ions created by ESI (Figure 1.11) the extensive *m*/*z* range required for mass analysis is effectively reduced, allowing spectra to be obtained for biomolecules with weights exceeding 100,000 Da.

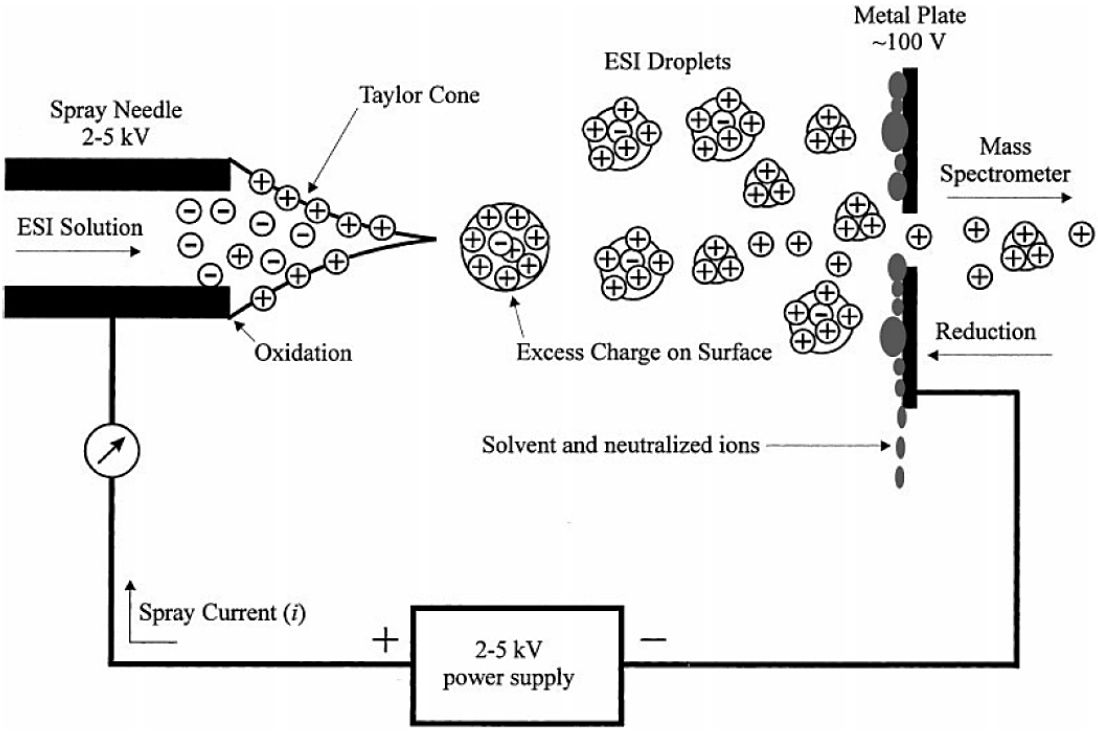

Figure 1.11: Schematic of electrospray ionisation process. The analyte solution is pumped through a needle to which a high voltage is applied. A Taylor cone with an excess of positive charge on its surface forms as a result of the electric field gradient between the ESI needle and the counter electrode. Charged droplets from the tip of the Taylor cone evaporate as they move towards the mass spectrometer inlet. Adapted from reference [167] with permission.

Since ESI generates gas phase ions from a sample solution it was realized in the mid-1980s that it could be used to interface capillary electrophoresis (CE) with MS [169]. As with other coupled separation techniques such as GC-MS and LC-MS, the primary advantage is the identification of analyte(s) due to both their differential separation and subsequent *m*/*z* analysis. For typical CE operation, the sample

analyte(s) first migrate through an electrolyte solution under the influence of an electric field being separated according to their ionic mobility after which they undergo MS analysis [170].

A rival "soft" ionisation technique, matrix-assisted laser desorption/ionisation (MALDI), for ionizing biological molecules and large organic molecules was invented by Tanaka. They shared the Nobel prize for Chemistry (2002) with Fenn "*for their development of soft desorption ionisation methods for mass spectrometric analyses of biological macromolecules*" [171]. The laser desorption method has undergone extensive development by Hillenkamp, Karas and co-workers [171,172]. MALDI relies on a matrix material having an absorption band that closely matches the energy (frequency) of the laser beam. The energy absorbed by the matrix is transfered to the analyte(s) causing it to desorb and ionise in concert [172]. High yields of the molecular ion are produced with few fragment ions. A major difference between MALDI and ESI is that MALDI produces far fewer multiply charged ions meaning a larger mass range mass spectrometer is required. Since MALDI is a pulsed technique it couples well to TOF MS which generally has a very large mass range (theoretically unlimited). The fundamental principles of MALDI can be traced back to the earlier developments of laser desorption (LD) ionisation in the early 1960s [173-175].

From the 1980s until the present day the application of MS to biological research has continued to grow. Improvements in technology and methodologies have made MS an essential tool in structural biology. In the 1990s a new hybrid instrument was developed by combining quadrupole and time-of-flight technologies (Q-TOF) [176]; this provided high sensitivity MS/MS which enabled low-femtomole/attomole-range biopolymer sequencing. The Q-TOF is similar to a triple

quadrupole except the last quadrupole section is replaced by a reflecting TOF analyser orthogonal to the ion beam. Since the TOF is used in the final stage, the ion signals are recorded in parallel and with improved resolution and mass accuracy.

A major instrument development in the 1990s was the invention of the orbitrap by Makarov [177]. The orbitrap is a high performance mass analyser similar in essence to the Kingdon trap (Kingdon, 1923) and quadrupole ion trap. The orbitrap has axially symmetric electrodes and uses electrostatic fields to create a quadro-logarithmic potential, given by equation (8);

$$U(r,z) = \frac{k}{2}\left(z^2 - \frac{r^2}{2}\right) + \frac{k}{2}R_m^2 \ln\left(\frac{r}{R_m}\right) + C \qquad (8)$$

where, r and z are cylindrical coordinates, C is a constant, k is field curvature, and R_m is the characteristic radius. Mass spectra are generated in a manner similar to FTICR MS whereby the image current from the dynamically trapped ions is converted from the time domain by Fourier transform. The exceptional performance benefits, in terms of high mass accuracy and high resolution, are due to the energy independence of injected ions and the high accuracy with which the field can be defined [178].

In 1997, MALDI TOF MS was first used for visualizing the spatial distribution of molecules [179] as opposed to SIMS. Imaging via MS provides further possibilities for MS investigation by combining molecular mass and spatial information for visualizing molecules on complex surfaces (see section V).

In 2004, a new trend in ionisation/sampling under ambient conditions led to rapid development in atmospheric pressure ionisation techniques [26, 180]. Ambient ionisation MS is different from earlier atmospheric pressure ionisation methods as it

utilizes direct sampling and ionisation of unmodified samples outside of the vacuum (i.e., at atmospheric pressure) with no/minimal sample preparation [181]. Ambient ionisation is particularly well-suited for portable and miniature systems which lend themselves to *in-situ* analyses such as point-of-care biomedical applications [182].

A new instrumental concept was recently demonstrated in 2011 [183-185], Distance-of-Flight (DOF) MS which is similar in essence to TOF yet quite distinct. Whereas TOF separates ions in time, DOF separates ions in space. This is achieved by measuring the spatial location of an ion at a specified time after the initial ion acceleration via a position sensitive detector. DOF MS, although still in its infancy as an MS technique, appears to offer the same benefits as TOF MS but with more possibilities due to the spatial distribution of ions and without the limitations related to temporal ion detection [186]. Figure 1.12 depicts a timeline summarizing some of the major innovations and developments in MS history to date.

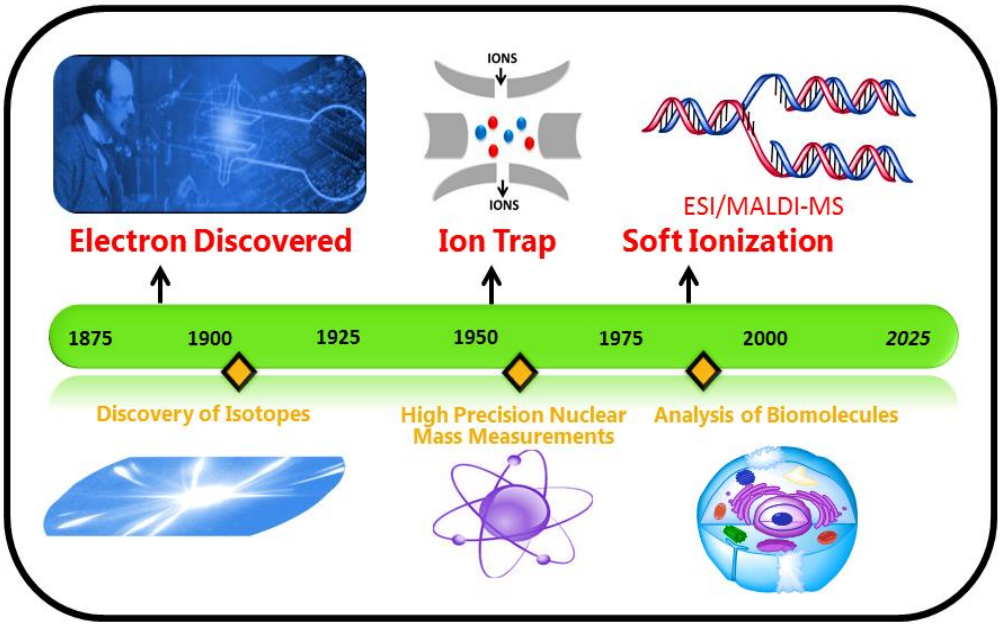

Figure 1.12: Summary timeline of major advances in MS.

1.5.0. Key Applications of Mass Spectrometry

Mass Spectrometry has developed into a field of science and technology that addresses important issues about the nature of matter on Earth and also in outer space. In this section we discuss a small selection of the remarkable MS applications reported in the past 100 years. A brief insight is given below into certain key applications that illustrate the strength and versatility of MS.

1.5.1. Isotope Ratio Mass Spectrometry

Isotopes are forms of an element (nuclide) where the numbers of neutrons are different leading to different atomic weights, for example ^{12}C and ^{13}C. Isotope ratio mass spectrometry (IRMS) uses MS methods to measure the abundance of isotopes in a given sample. A significant application of IRMS occurred during the Manhattan project [187] for the enrichment of Uranium [188]. MS was used at different stages of making the first atomic bomb which was later used during World War II [187]. During the enrichment process MS was used as means to detect, quantify and isolate ^{235}U. It was also utilized for online monitoring and analysis of the residual air contaminates at the Oak-Ridge gaseous diffusion plant during the separation of Uranium isotopes [187].

Knowledge of precise nuclear masses gives information regarding the binding energy of atomic nuclei. The binding energy can be determined by measuring the mass of the composite system as well as those of its building blocks and reflects all the nucleonic interactions in the nucleus. As such high precision MS is a very important research tool for many scientific endeavours such as in nuclear physics [189]. Previously it was identified that only about a quarter of all the

possible nuclei lying between the nuclear drip lines have had their masses measured [190]. This is particularly true for heavy, highly neutron-rich, nuclei. High precision mass measurements can inform nuclear-mass models and reduce ambiguity in current models which rely heavily on theoretical calculations [191]. The pursuit for higher precision measurements is illustrated in Figure 1.13 which shows the relative precision, $\Delta Q/Q$, for various measurements where Q is the measured Q_{EC} value (total transition energy) and ΔQ is the quoted uncertainty for super-allowed decay experiments. The Q_{EC} values for super-allowed transitions were measured with nuclear reactions (typically (p, n) or (^{3}He, t) on β decay daughter nuclei) until the advent of the on-line Penning trap MS technique in 2005 [192-205]. The relative precision for such measurements has reached ~7 x 10^{-6} by using the Penning trap based on MS approach. This has undergone several refinements since its inception, such as the implementation of ion-motion excitation using Ramsey's method of time separated oscillatory fields [192-205]. This has led to the widespread uptake of this technique for high-precision nuclear studies [199-202].

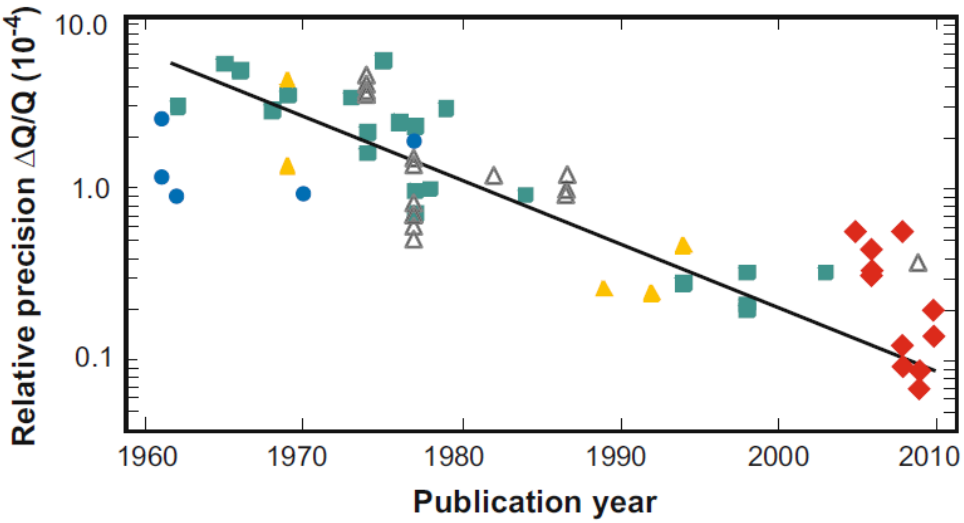

Figure 1.13: The relative precision, $\Delta Q/Q$, for Q_{EC}-value measurements of super-allowed transitions is plotted against their publication date, where Q is the measured Q_{EC} value and ΔQ is its quoted uncertainty. The data encompasses the super-allowed transitions from ^{10}C, ^{14}O, ^{26}Al^{m}, ^{34}Cl, ^{38}K^{m}, ^{42}Sc, ^{46}V, ^{50}Mn and ^{54}Co. Each point is identified by the experimental method used in the corresponding measurement: solid green squares denote (p, n) reactions; open triangles, (^{3}He, t) reactions; solid blue circles, two-nucleon transfer reactions (p, t) or (^{3}He, n); solid yellow triangles, combined (p, γ) and (n, γ) reactions; and solid red diamonds, Penning-trap measurements. The line illustrates the decreasing trend. Adapted from reference [197] with permission.

The ability to measure different isotopes in mixtures with high sensitivity and precision using IRMS has enabled the detection of minute differences of naturally occurring isotopic abundances [206]. IRMS has been used for measurement of different chemical composition of matter in the solid, liquid and gaseous phase. High performance magnetic sector instruments, optimized for ultra-high sensitivity and precision, are often utilized in IRMS experiments for the analysis of naturally occurring trace level isotopic abundance [207]. IRMS measurements have become an analytical standard in a wide range of scientific endeavours, such as archaeology, forensics, health care and food science. For instance in forensics and archaeology, IRMS is often used to provide evidence for the origin of a substance. For example, a model has been developed relating the geographic origin of humans from the 48

contiguous North American states based on the stable isotope composition of their scalp hair compared with local tap water [207]. The isotopically lightest tap waters for δ^2H and $\delta^{18}O$ were from northern Montana and the heaviest waters were sampled in southern Oklahoma. Figure 1.14 shows the isotopically heaviest scalp hair is expected to occur in the southern parts of the United States. IRMS is also applied in the food industry were isotope ratios of $^2H/^1H$, $^{13}C/^{12}C$ and $^{18}O/^{16}O$ are routinely screened as a means of quality control to detect food adulterations. This includes detecting the addition of synthetic additives, artificial aromas and sugar to fruit juices, and to confirm (or refute) the declaration of origin for food/drink [208].

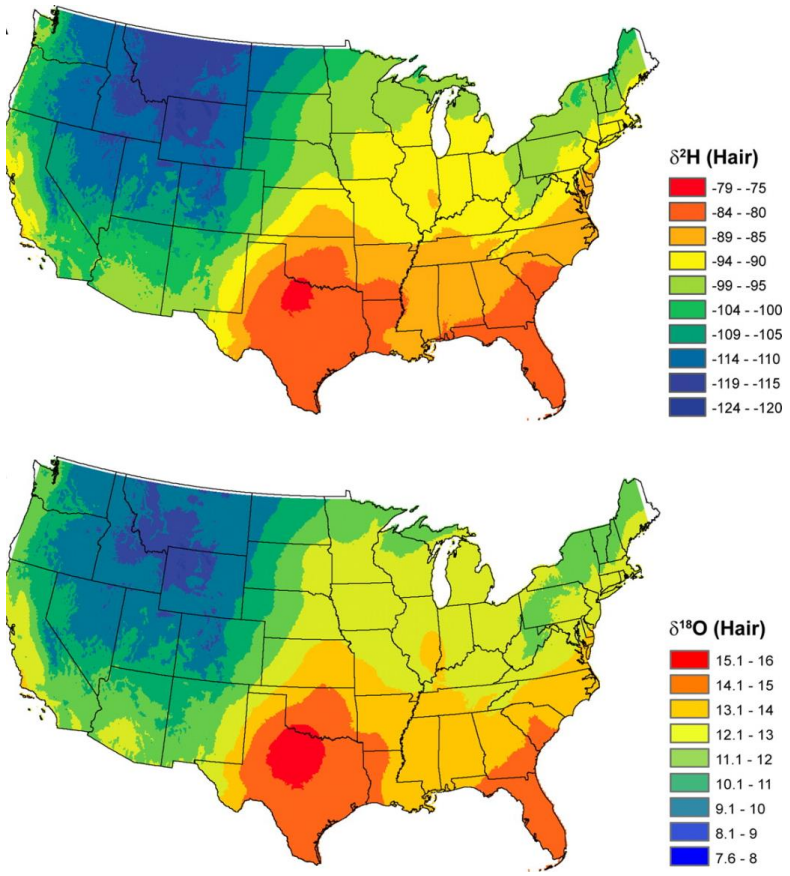

Figure 1.14: Maps of the predicted (b) average H isotope ratios (δ^2H_h) and (b) average O isotope ratios ($\delta^{18}O_h$) of human scalp hair across the coterminous United States. Reproduced with permission from reference [207].

For the analysis of naturally occurring sample analyte(s) with long half-life isotopes occurring at ultra-trace levels, accelerator mass spectrometry (AMS) is the method of choice. This is because it provides ultimate sensitivity, capable of measuring individual atoms and measuring nuclides with a dynamic range of ~10^{-15} relative to the major stable isotope. AMS utilizes a high energy accelerator to accelerate ions to high energies up to tens of megavolts (MV) and is designed to suppress background ions (isobars) using filtering techniques such as degrader foils common in high energy nuclear physics. Highly sensitive single-ion counting detection methods are used such as solid state Silicon detectors and gas ionisation chambers [209].

The first use of an accelerator with a mass spectrometer was in 1939 for the separation of ^{3}He from ^{4}He using a cyclotron [209]. Building on this work during the 1970s researchers sought to develop AMS for radiocarbon dating for the determination of ^{14}C/^{13}C ratio [210] which is the most widespread application of AMS (Cawley and Flenker, 2008). The ^{14}C/ ^{13}C ratio is commonly used for age determination for archaeological purposes and artefacts [210]. Recently there has been an increase in the application of AMS in the field of biomedicine and for unknown masses of neutron-rich nuclei [211]. In geology, quantification of long-lived radionuclides formed by the impact of cosmic rays was observed for the first time by Philips and co-workers [212]. For example the Arizona meteor crater age was determined using the ^{36}Cl content from the surface of ejected rocks which had been shielded from cosmic rays while underground [213,214].

Use of performance enhancing drugs by athletes in sports is under increasing investigation. The isotopic ratio of ^{14}C/^{13}C is routinely used to test banned substances in urine and blood of athletes [214]. Detection of ‘designer’ drugs [215],

like tetrahydrogestinone (THC), using IRMS with isotopically labelled stable isotopes at trace levels (<parts per trillion) in urine and blood has been demonstrated [216]. Steroidal hormone levels in athletes can also be verified using IRMS [217]. For instance, the $\delta^{13}C$ values of exogenous steroids are significantly reduced compared to those of the endogenous steroids produced naturally in the body [218]. These lower values can be detected in a urine sample for both epitestosterone and for metabolic degradation products such as androsterone and etiocholanolone [219-229].

1.5.2. Mass Spectrometry in Life Sciences

The trigger point which led to a surge of MS-based research activities in life sciences was the development of ESI [167] and MALDI [171] during the 1980s. These ionisation methods combined with innovation in instrumentation led to the widespread application of MS in biology and medicinal chemistry [230]. MS is the most comprehensive and versatile tool in large scale proteomics [231]. The study and understanding of genomes (and proteins) is required for effective drug development.

There are two general approaches to proteomics analysis depending on the application and the complexity of the sample (Figure 1.15). 'Bottom-up' analysis requires that proteins are enzymatically digested into peptides and this method is popular for complex, large scale analyses [232]. The 'top-down' approach analyses intact proteins and is a popular method for identification and structural analyses [233]. Proteomic studies include a variety of analyses such as protein identification, protein-protein and nucleic acid interactions, peptide-peptide interactions [234], *de*

novo peptide sequencing [235], post-translation modifications [236], and signalling pathways in which proteins participate [237].

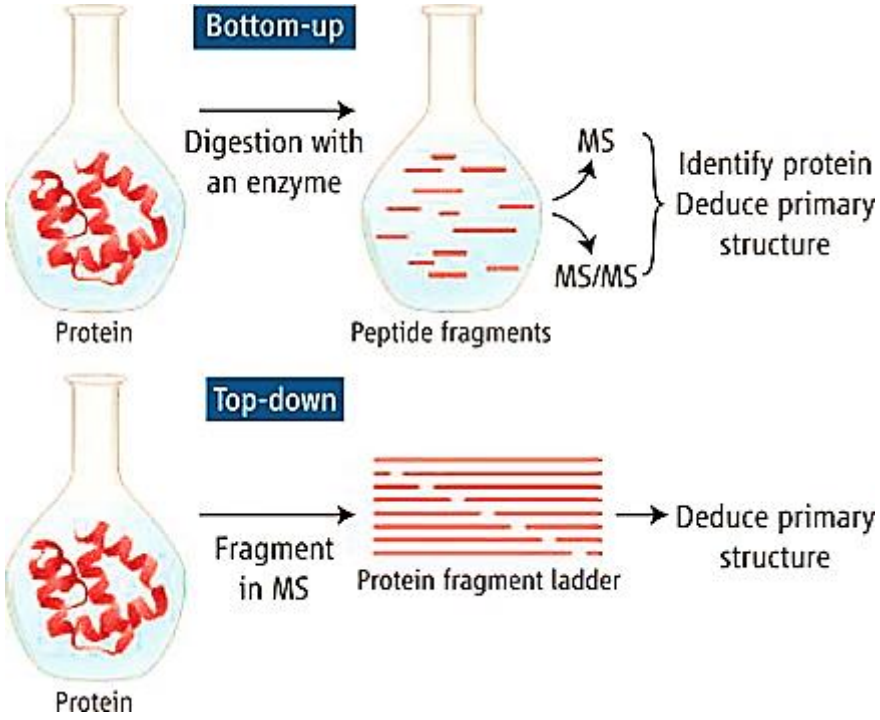

Figure 1.15: Bottom-up approach (top), proteins of interest are digested in solution with an enzyme such as trypsin, and the resulting peptides are analysed in the gas phase by mass spectrometry. Top-down approach (bottom), intact protein ions are introduced into the gas phase and are fragmented and analysed in the mass spectrometer, yielding the molecular mass of the protein as well as protein ion fragment ladders; this information can be used to deduce the complete primary structure of the protein. Both methods make extensive use of correlation of the mass spectrometric data with protein and whole-genome sequence databases. Adapted from reference [237] with permission.

An example of this is a recent study seeking to identify a biomarker for the early detection of chronic heart failure [237] where MS was used to assess post-translational modifications from proteins extracted from normal and diseased cardiac tissues. Post-translational modifications are associated with critical signalling events during disease progression. These were quantified and then correlated with disease

phenotypes for potential biomarker identification (Figure 1.16). Discovery of biomarkers with high specificity and accuracy are important in clinical practice to allow for early disease detection which allows intervention strategies to delay or prevent disease progression [238].

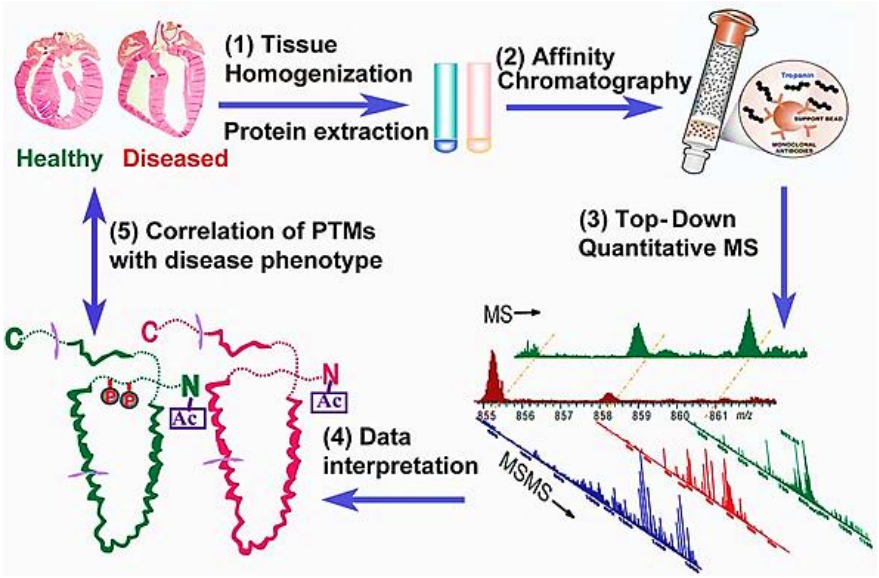

Figure 1.16: Schematic representation of top-down quantitative proteomics methodology for the comprehensive analysis of post-translational modifications (PTMs) in whole proteins extracted from normal and diseased tissues. The five steps include: (1) – (2) Sample preparation – extraction and purification. (3) Top-down quantitative MS analyses. (4) Data interpretation. Protein sequences were characterized and their PTMs detected, identified, quantified, and mapped to single amino acid residues. (5) Correlation of PTMs with disease phenotypes. Adapted from reference [237] with permission.

1.5.3. Imaging Mass Spectrometry

It is not common to think of MS as a means of providing spatially resolved information. However, imaging mass spectrometry (IMS) is a technique based on mass spectrometry that can be used to obtain a two-dimensional (2D) chemical map for visualizing surfaces of different sample matrices. A visual image of the

component distribution of molecules in a sample can be obtained from simultaneous measurements of spectra and spatial time information [239, 240]. In this way, the high specificity and sensitivity of MS is harnessed for direct mapping of the spatial arrangement of molecules. Other imaging techniques, such as scanning electron microscopy and atomic force microscopy, deliver high performance in terms of spatial resolution but lack chemical information. Those that can provide chemical information, such as fluorescent labelling microscopy, also require prior knowledge of the sample. Recent applications combine one or more of these imaging techniques with MS imaging to give multi-dimensional information [241].

Castaing and Slodzian [242], were the first to recognize the potential for an ion-optical collection system which could be used to interpret the spatial profile of desorbed ions from a surface [242]. Rapid commercialization has meant that SIMS imaging has become common place for quality control, surface profiling and process monitoring [243]. However, conventional SIMS imaging is not well suited for analyses of biological macromolecules because the secondary ion beam can break the structure where it is essential that lateral organization of the sample is preserved [144]. For such cases, MALDI imaging and desorption electrospray ionisation (DESI) imaging [245-248] are more commonly used; see Table 1.4 for further details. DESI imaging experiments are performed in ambient conditions requiring little sample preparation but suffer from relatively poor spatial resolution. MALDI imaging has greater spatial resolution than DESI but is typically carried out *in vacuo* and requires special sample preparation to achieve high quality images.

	SIMS	MALDI	DESI
Working procedure	Beam bombardment in high vacuum	Soft ionisation with laser *in vacuo* or at atmospheric pressure	Soft ionisation at atmospheric pressure
Target surfaces	Elements, some small biological molecules	Biological macromolecules, drugs	Biological macromolecules, drugs
Spatial resolution	Low nm	Low µm	µm

Table 1.4: Major Imaging Mass Spectrometry Methods.

The limitation of SIMS for biological analyses was addressed by Prof. Caprioli and co-workers who used MALDI-MS for the imaging of peptides and proteins [[245-249]. Cooks and co-workers have also applied DESI MS imaging to a range of chemical classes including biological tissues and drugs (Figure 1.17) [250].

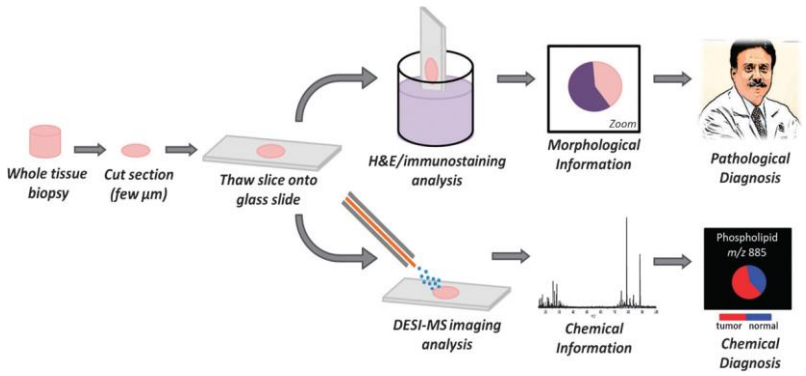

Figure 1.17: Overview of tissue processing to achieve a diagnosis by traditional pathological staining techniques and by DESI imaging mass spectrometry. Reproduced from reference [248] with permission.

There are two general approaches to IMS referred to as microprobe and microscope modes (Figure 1.18). The more common microprobe mode uses a highly focused ionisation source to raster across the sample surface measuring the MS response for each pixel of the image. The image resolution is limited by the spot size of the ionizing beam. A trade-off exists between pixel resolution and analysis time. Reduced analysis time leads to increased throughput and is particularly advantageous for time-depleting samples. The alternative microscope approach uses a defocused

ion beam (larger spot size), utilizing a position-sensitive detector [250,251]. The position-sensitive detector allows parallel acquisition of ion arrival time and position. The major advantage is increased sample throughput. The image resolution is not limited by the ion beam spot size but depends on the accuracy of the mass spectrometer ion optics and the capability of the position-sensitive detector.

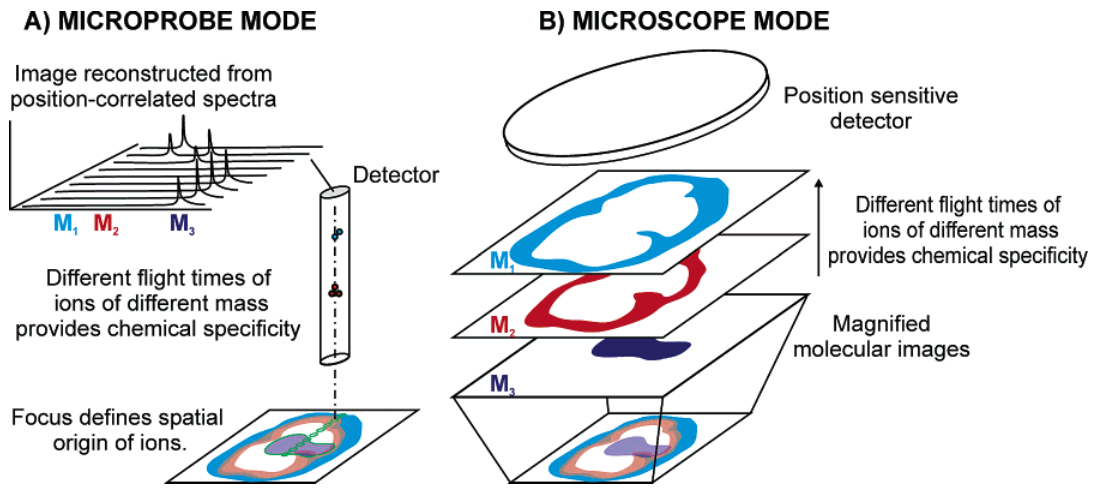

Figure 1.18 : Two different approaches to imaging mass spectrometry: (a) collects mass spectral information from an array of designated positions to reconstruct a molecular image after completion of the experiment; (b) a two-dimensional position sensitive detector acquires *m*/*z* and position information in parallel. Reproduced from reference [249] with permission.

The evolution of IMS is giving way to the realization of routine three-dimensional (3D) imaging of biological samples where multiple 2D mass spectrometric images are combined, using image processing techniques, to construct a 3D map of molecules throughout a sample structure [251]. 3D depth-profiling using SIMS has been in use for several years and 3D visualization has been demonstrated with DESI [252] and MALDI [253-255] imaging techniques.

1.6.0. Future Trends

1.6.1. Miniature Mass Spectrometry for *in-situ* Analyses

Traditionally, MS analyses have been limited to a laboratory setting due to the constraints of weight, size and electrical power. However, in the last 20 years there has emerged an increasing trend to take the mass spectrometer beyond its laboratory setting and this continues to be a growing area of research and development. Since a mass spectrometer is comprised of several sub-systems (Figure 2.1), the whole system miniaturization is complex. Improvements in mass analysers, vacuum pumps, detection systems, and control electronics have allowed a reduction, in weight, power requirements and the entire footprint of the whole mass spectrometer system [256]. Self-sustainable portable MS systems have been developed for the time of flight [258], quadrupole [259], and ion trap mass analysers [260-266].

The most common miniaturized mass spectrometers commercially available are quadrupole and quadrupole ion trap (QIT) [260-266]. However, QITs have distinct advantages for miniaturization over other mass analysers; these include operation at higher pressure and capability for MS/MS analysis in a single device [260-266]. High sensitivity, approaching that of commercial instruments, can be obtained using high performance detectors [267]. The development of miniature mass spectrometers, with tandem analysis capability, has opened up a wide range of applications in field chemical analyses, e.g., on the battlefield, in the factory, and on the surgical ward [268,269]. The ability to perform multi-stage MS/MS using a single analyser facilitates analyte elucidation and structural characterization. This

provides analyte(s) identification confirmation (via fragmented ions) and enhanced detection limits by improved signal-to-noise ratio.

MS/MS functionality from a single device has been demonstrated for a portable ion trap mass spectrometer used to monitor cocaine, as shown in Figure 1.19 (a-b). This portable backpack MS system weighs 10 kg and is coupled to a low-temperature plasma (LTP) ambient ion source [268,269]. The capability of this small instrument has been demonstrated in the detection and quantification of chemical warfare agent (CWA) stimulants, illicit drugs, and explosives at trace level concentration (nano-gram) directly from surfaces in near real time. In Figure 1.19 (c), the same miniaturized mass spectrometer is packaged for clinical/medical applications. In this case multi stage MS/MS scans are implemented to obtain the intensities of the fragment ions from the analyte and an internal standard; for quantitative analysis of (i) anti-depressant drug amitriptyline in blood samples, and (ii) fungicide thiabendazole on the surface of an orange peel (Figure 1.19 (d)).

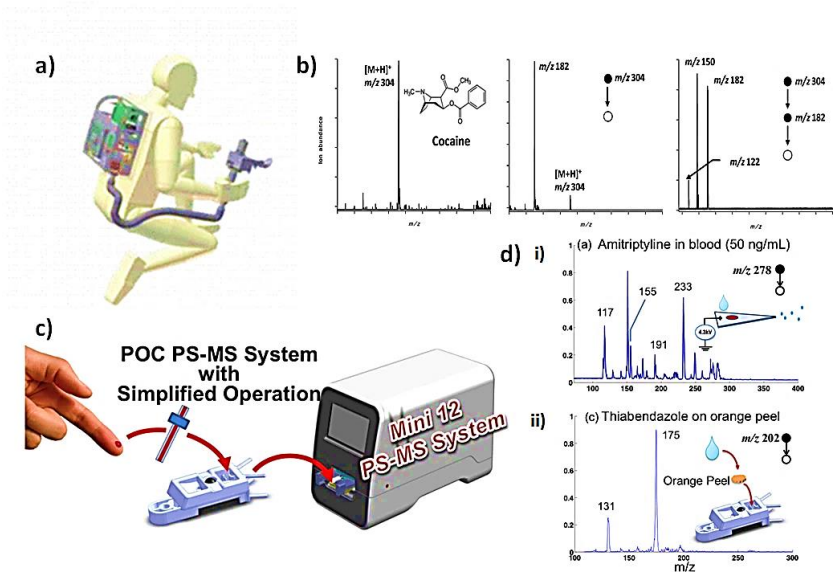

Figure 1.19: *In-situ* mass spectrometry using a system that provides a simplified operational protocol, (a) Miniature mass spectrometer composed of two sections, a backpack section that houses the vacuum system and control electronics and hand-held head unit with an integrated LTP source for geometry-independent sampling/ionisation probe, (b) Multiple-stage product ion scan (MS/MS/MS) demonstrated using 100 ppm of the model compound cocaine, (c) Miniaturized desktop point-of-care (POC) mass spectrometer system coupled with ambient paper spray for medical applications, (d) MS/MS spectra of (i) 50 ng/mL of amitriptyline in blood recorded with paper spray ionisation. (ii) MS/MS spectra of thiabendazole on an orange peel obtained using paper spray ionisation. Adapted from reference [268 and 269] with permission.

1.6.2. Ion Soft-Landing and Material Synthesis using Preparative Mass Spectrometry

Much of the work reviewed in this report has been centred on the primary function of MS as a tool for chemical analyses based on detection and quantification of ions according to their *m/z* ratio. However, MS also shows promise for material synthesis. Ion soft-landing is characterized by deposition of intact species on surfaces at low kinetic energies (Figure 1.20) which precludes the fragmentation of the incident species [300]. This capability of MS has been demonstrated for highly

controlled (atom by atom) deposition of nano-particles on different materials [301-303]. The soft landing technique was first reported in 1977 for the reaction of low energy sulfur containing ions on a lead surface [304]. Since then intact deposition has been demonstrated with clusters, organometallics and biologically active molecules (such as proteins, peptides (see Figure 1.20), DNA, viruses) [305-310]. This shows promise for applications in areas such as catalysis, thin film preparation, molecular electronics, preparation of protein microarrays, and biomaterial development.

Ion soft landing has certain advantages over other methods of surface modification (such as molecular beam epitaxy, physical vapour deposition, etc.) including, high selectivity and sensitivity of the deposited species, inherent ion beam focusing and mass selectivity. However, the major limiting factor is the relatively low ion currents (~10^{-9} A) produced which prevents bulk material synthesis [300].

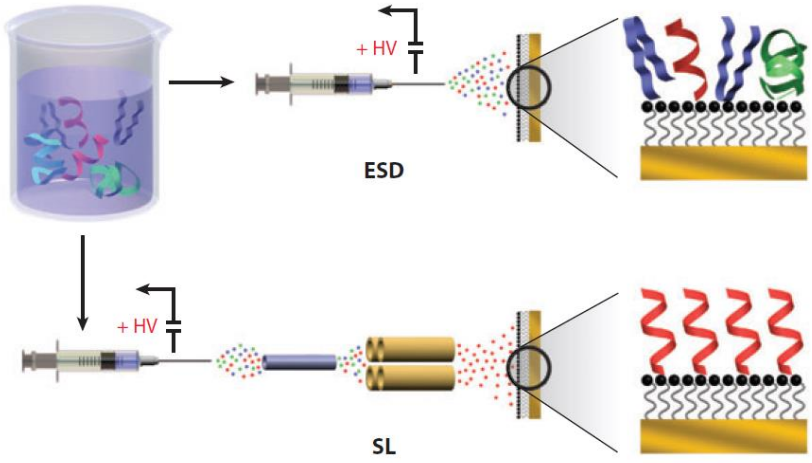

Figure 1.20: Schematic drawing of (top) electrospray deposition (ESD) and (bottom) soft landing (SL) of peptide ions on self-assembled monolayer (SAM) surfaces. ESD of $AcA_{15}K$ from solution results in the formation of a peptide layer dominated by the β-sheet structure, and a stable α-helical peptide layer on SAM surfaces is formed by SL. Reproduced with permission from reference [301].

1.6.3. Mass Spectrometry for Rapid Biological Tissue Analyses

MS is also emerging as a tool for rapid clinical diagnostics and for surgical treatment of cancer. Coupling the high sensitivity, specificity and speed of the mass spectrometer with ambient ionisation techniques has the potential for rapid tissue analysis allowing immediate medical decisions to be made. A recent study has demonstrated the potential for the use of a traditional needle biopsy to act both as the agent for extracting biological fluid from animal tissue, and as the medium for spray-based ionisation. By applying a high voltage to the biopsy needle and a solvent for chemical extraction, highly specific molecular information was acquired being available within 1 minute of the biopsy [311].

Ambient desorption MS methods are well-suited for *in-situ* analyses. Rapid Evaporative Ionisation Mass Spectrometry (REIMS) is an emerging technique for *in vivo* ionisation of tissue constituents. REIMS allows rapid evaporation of biological materials with MS analysis to perform *in-situ* tissue analyses in near real time. The significance of REIMS lies in its potential use in cancer surgery being coupled with surgical methods. Tissues thermally ablated produce aerosols and the heat dissipated during the process generates charged species. The generated ions and aerosols created during the process are transported pneumatically from the surgical site to the vacuum system of the mass spectrometer for analysis [50].

REIMS has been coupled with electro-surgery equipment and used in the operating theatre for cancer diagnostics (known as “iKnife”). This novel application of MS uses standard electrosurgical methods as a means of producing gas phase ions from evaporating tissue as it is resected. The mass spectrometer analyses the tissue

vapour and uses multivariate statistical methods coupled to differentiate between histological and histopathological tissue types (Figure 1.21). The technique has potential to provide almost instantaneous feedback for the surgeon to ensure that all malignant tissue is efficiently and effectively removed during oncosurgical procedures. The technique has been tested collecting data *in vivo* from 81 patients who underwent surgical interventions which were then analysed offline. Binary classification (cancer or healthy) of all cases resulted in a sensitivity of 97.7%, a specificity of 96.5%, and low false-positives (3.5%) and false-negatives (2.3%) for the technique [312].

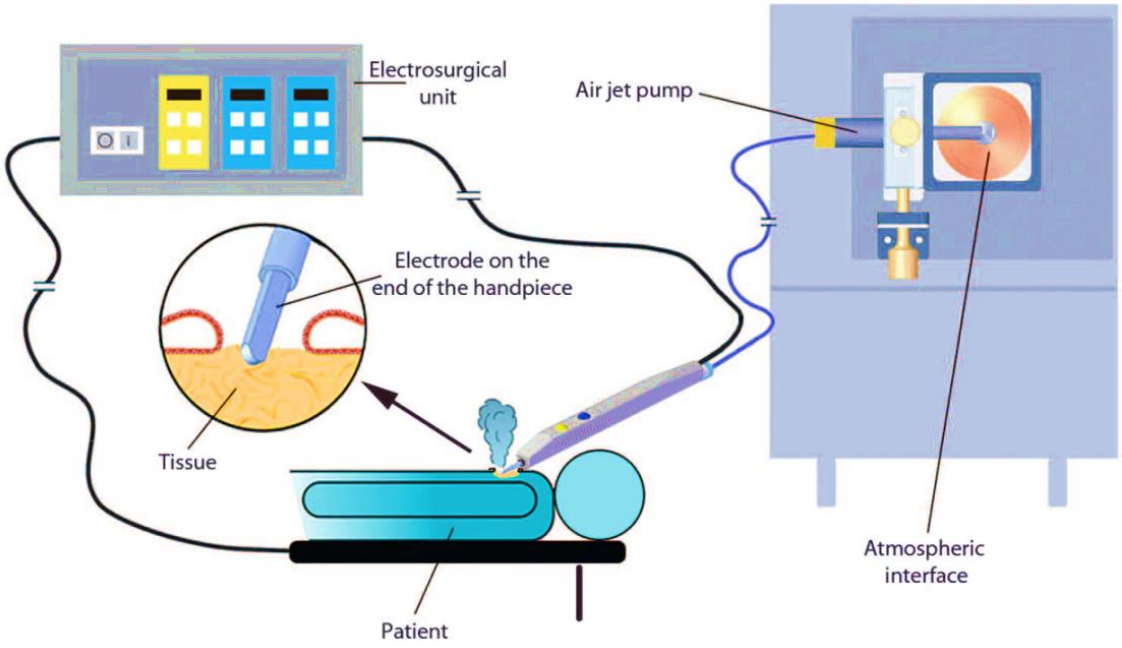

Figure 1.21: Schema of REIMS instrumentation and data collection showing use with monopolar electrosurgery. Adapted from reference [282] with permission.

1.7.0. Conclusion

A century has passed since the foundational work of Thomson who is widely regarded as the pioneer of MS. Thomson realized the enormous potential of the technique exemplified by his writing in 1913 [82], *"there are many problems in Chemistry which could be solved with far greater ease by this method."* Judging by the scope and extensive use of MS in the present day, Thomson may have understated the potential. MS is today an established *bona fide* clinical tool, a ubiquitous and indispensable research instrument with an extremely wide range of applications. Arguably, no other device has contributed to so many fields over the past 100 years.

The path ahead for MS seems certain to include much more emphasis on multiplexed (orthogonal) measurements and instrumentation especially in the realm of MS imaging. Multidimensional imaging e.g., MS with X-Ray computerized tomography (CT) and Magnetic Resonance Imaging (MRI) is currently an active area of research [241, 283]. Further developments in MS-based proteomics as a tool for new drug discovery and/or biomarker determination could lead to personalized drug development to inactivate specific proteins linked with particular disease conditions [284]. Due to the increasing rate and amount of data acquisition in MS, developments in the handling and processing of 'big data' [285, 286] will play a key role in the future of MS.

The need to analyse many more samples in the areas of biomedical, clinical, environmental and public safety will require higher throughput, onsite (point-of-use) measurements and smaller, more specialized instrumentation. The capabilities of ambient ionisation methods are particularly well suited to these high volume

applications in that sample preparation is minimized/removed [24]. Advances in MS miniaturization, portability, versatility and ruggedness have led to mass spectrometers being deployed in a variety of harsh environments [287] not limited to our own planet [8, 9]. Future developments in MS will not be limited to its primary function as an analytical method. Soft landing MS has become a topic of substantial interest as a technique for material synthesis due its potential to enable highly controlled preparation of materials [271, 280].

The presence of toxic and potentially hazardous compounds in our environment, forensic settings, and the increasing need to monitor biological compounds produced in *vivo,* demands the development of on-site analytical systems with the ability detect a wide range of analyte(s) *in-situ* with little or no sample preparation. Despite the extensive use of MS, it is not an ideal method for all analyses; sample preparation before introduction into a mass spectrometer can be laborious and time-consuming, and many applications are limited by the inconvenience of *ex-situ* MS analysis [313-316]. Furthermore, samples are always transported to centralized laboratory for analysis. The need for on-site, instant analysis of suspected toxic and hazardous compounds in our environment is thus a clear and present need for the first responders in the homeland security, defence, forensics, and environmental contexts.

1.8.0. Research Objectives

The overall goal of this research was to investigate the possibility of *in-situ* (real time) on-site detection for a wide range organic chemicals in their native environment outside the laboratory setting using two ambient ionisation techniques

(i.e. desorption atmospheric pressure chemical ionisation (DAPCI) and paper spray (PS) coupled to a portable mass spectrometer. Real-time on-site analysis at the source using ambient MS means, in this case, that the analysis and data acquisition must be done instantly or rapidly (in less than 2 minutes) under atmospheric pressure conditions, in an open environment and with little or no sample preparation. The motivation behind this work was the need for immediate detection of potentially toxic and hazardous chemical substance on-site. Such rapid response would be important in case of national defence, homeland security, forensics and environmental monitoring. Because the analyte(s) of interest are detected and characterized *in-situ* at the source, then cost savings in time, sample transport and storage are anticipated. Together with careful experimental observations, application of these ambient ion sources to condensed phase analyte(s) in their native environment allows for better understanding of their ionisation mechanism and a wider reach of analytical application.

1.8.0. Research Contribution

My research contributions to analytical science instrumentation and engineering in mass spectrometry are summarised as follows:-

(i) Two ambient ionisation mass spectrometry technologies i.e. desorption atmospheric pressure chemical ionisation (DAPCI) and paper spray ionisation (PS) have been successfully coupled to a portable mass spectrometer and deployed for on-site field applications for the first time.

(ii) A new area of mass spectrometry analysis has been opened, in which analyte(s) can be analysed *in-situ* in their native environment with little or no sample preparation.

(iii) Because samples can be analysed *in-situ* without sample preparation, the developed analytical methods can will allow non-specialists or first responders to use MS in the field to obtain immediate results. As already implicitly noted, this fundamental work will allow *in-situ* analysis of complex condensed phase samples in their native environment with little or no sample preparation.

(iv) A method for *in-situ* chemical derivation of primary amine corrosion inhibitor formulations in water samples using paper spray mass spectrometry at atmospheric pressure has been developed.

(v) Fundamental of *in-situ* ion generation under ambient conditions, has been demonstrated.

(vi) Mass spectrometry analysis has been extended beyond the laboratory environment, using DAPCI and PS ionization methods coupled to a miniature mass spectrometer.

The major advantage of such developments is the provision of data in real-time (or near real-time) at the point of interest allowing key management decisions to be taken in a timely manner. In addtion there would be advantages relating to the chain of custody. By effectively taking the lab to the sample rather than the sample to the lab, sampling time and costs are significantly reduced.

In the next chapter (Ch 2), the *in-situ* analysis of petroleum oil hydrocarbons using DAPC ionisation is investigated and the DAPCI ionization mechanism is dicussed.

1.9.0. References

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Chapter 2 : Observation of Protonated and Molecular Ion Species in DAPCI

2.0 Overview

Following the pioneering work of Sir JJ Thompson, obtaining molecular mass information for numerous small molecules presented a challenge. This challenge was overcome by electron impact (EI) ionisation. However, because of the short lived vertical transitions associated with EI [1, 2], significant extensive fragmentation of the analyte(s) is always observed which tended to obscure molecular weight information. Thus we are often forced to resort to softer ionisation methods such as chemical ionisation (CI) [3], Electrospray ionisation (ESI) [4] and matrix assisted laser desorption ionisation (MALDI) [5]. Recently the advent of softer ambient ionisation methods, such as desorption electrospray ionisation (DESI) in 2004 [6], and direct analysis in real time (DART) in 2007 [7], has led to an increasing importance of research into the generation of gaseous ions under ambient conditions. Ambient ionisation methods based on atmospheric pressure chemical ionisation (APCI), and methods that employ a glow [8] or corona discharges [9, 10] are always utilized. Although ion formation occurs when samples are exposed to discharges, the overall mechanism of ambient ionisation methods remains poorly defined [11]. In this chapter the application of the desorption atmospheric pressure chemical ionisation (DAPCI) ion source to the *in-situ* analysis of petroleum oil hydrocarbons is presented, and the ionisation mechanism of a novel ambient ionisation source, (DAPCI) is inferred. Conditions were chosen for the DAPCI experiments to control whether protonated molecules are generated via proton transfer, or molecular ions are generated via electron transfer. The protonated

molecule $[M+H]^+$ and the hydride abstracted $[M-H]^+$ form were observed when using an inert gas, typically nitrogen, to direct a lightly ionised plasma generated by corona discharge onto the sample surface in air. The abundant water cluster ions generated in this experiment react with condensed-phase functionalized model compounds and their mixtures at or near the sample surface in the open air. On the contrary, when naphthalene was doped into the DAPCI gas stream, its ionised radical cation served as a charge exchange reagent, yielding molecular radical cation $M^{+\bullet}$ of the model compounds. This mode of sample ionisation provided mass spectra with better signal/noise ratios and without unwanted side-products. Operating under the conditions just described (that favour protonation and charge transfer reactions), the DAPCI technique was applied to *in-situ* characterization of the various petroleum constituents (hydronaphthalenes, thiophenes, alkyl substituted benzenes, pyridines, carbazoles, indole, aniline, fluorenes, and polycyclic aromatic hydrocarbons (PAHs)) under ambient conditions without sample preparation. These conditions also extended the applicability of DAPCI to petroleum constituents which could not be analysed through proton transfer (e.g. higher molecular PAHs such as chrysene). The thermochemistry governing the individual ionisation processes is discussed, and a desorption/ionisation mechanism is inferred.

2.1 Introduction

Mass spectrometry (MS) is the gold standard method for trace detection of a wide range of analyte(s) due to its high sensitivity and specificity; in additionthrough tandem mass spectrometry (MS/MS), applicability to complex mixture analysis can be achieved [12, 13]. As the utilisation of MS has increased, so has interest in its

applicability to *in-situ* analysis of samples in the open environment. *In-situ* experiments require suitable portable instrumentation capable of MS/MS [14-16] as well as ionisation methods that operate under ambient conditions without requiring prior sample preparation. Such methods will allow non-specialists to use MS in the field and to obtain immediate results.

The advent of ambient ionisation techniques has enabled the mass spectrometric analysis of chemical compounds from unmodified surfaces in their native environments [9-15]. The most commonly used ambient ionisation methods are the spray-based method of desorption electrospray ionisation (DESI) [11-16] and the plasma-based method known as direct analysis in real time (DART) [17]. The analytical capabilities of the various ambient ionisation methods have been demonstrated. Through their application to a wide range of samples in biomedicine, tissue imaging and bio-fluid analysis [18-20], chemical imaging and forensics [21], environmental monitoring and food safety [22], and in pharmaceutical science as well as in transportation security [23].

Desorption atmospheric pressure chemical ionisation (DAPCI) [24] is another example of a plasma-based ambient ionisation technique but one which is relatively under-utilized compared to others [7], [25]. DAPCI is derived from atmospheric pressure chemical ionisation (APCI) [26], although DAPCI produces ions from solids in the open air instead of from solutions or vapours. In DAPCI, a corona discharge is generated by applying a high DC voltage to a sharp needle and the reagent ions produced are directed pneumatically towards a surface using a high velocity carrier gas (e.g. nitrogen). In a typical DAPCI experiment, the analyte(s) of interest is desorbed and ionised directly from the surface, presumably by a two-step mechanism involving thermal desorption followed by gas-phase ionisation [24].

Earlier experiments demonstrated DAPCI to be more effective at ionizing compounds of moderate to low polarity and hence significant vapour pressure [4]. Performing DAPCI experiments in ambient air generates protonated water cluster ions which facilitate analyte(s) ionisation [17], under ambient conditions without requiring prior sample preparations.

Using water clusters as the primary ion species, DAPCI ion sources have been used in agriculture and food chemistry to characterize various natural products [18], and in the detection of explosives, herbicides and simulants on a variety of surfaces, including skin [17]. Using methanol/water vapour as the DAPCI carrier gas, the stimulant dimethyl methyl phosphonate (DMMP) displayed low detection limits using DAPCI compared to DESI [17]. Furthermore, peroxide explosives have been identified at lower detection limits using alternative reagent ions, specifically ammonium reagent ions instead of methanol/water vapours [19]. Aside from moderating the degree of proton transfer by selecting appropriate solvent vapours for DAPCI, charge exchange reagents (e.g. benzene and fluorobenzene) can also be doped into the gas stream to initiate electron transfer reactions [20, 21].

Analogous conditions have been found to be useful in DART for the analysis of analyte(s) such as hydrocarbons, which have low proton affinities and cannot be effectively protonated by protonated water clusters [21]. Charge exchange is also the basis of a related ambient ionisation method, termed desorption charge exchange ionisation (DICE) [22] which differs from DAPCI in that it uses a stream of charged droplets but is related in that it uses an easily ionised solvent like toluene.

In this chapter, the generation of molecular cations $M^{+\bullet}$ and protonated and de-protonated molecules $[M+H]^+$, $[M-H]^+$, using DAPCI is investigated and applied to the analysis of different petroleum crude oil and fuel constituents (i.e.

hydronaphthalenes, thiophenes, alkyl substituted benzenes, pyridines, carbazoles, indole, aniline, fluorenes, and polycyclic aromatic hydrocarbons and *n*-alkanes). Other than the normal DAPCI experiment (operating under ambient conditions), a head space vapour of naphthalene was doped into the DAPCI carrier gas as the charge exchange reagent for the electron transfer reactions. Two ionisation modes were used to sample petroleum hydrocarbon constituents. Radical cations $M^{+\bullet}$, protonated and de-protonated molecular ion species $[M+H]^+$, $[M-H]^+$ were generated during electron and proton transfer ionisation modes, respectively (as illustrated in Figure 2.1). The electron transfer process often produces a simpler mass spectrum. The electron transfer ionisation mode also extended the range of DAPCI applications to higher molecular compounds such as polycyclic aromatic hydrocarbons that could not be ionised via proton attachment. In addition to protonation, other reactions such as hydride abstraction (sometimes followed by hydration of the resulting deprotonated/hydride subtracted $[M-H]^+$ ions as well as oxidation $[M+O]^+$ of certain hydrocarbons. Side reactions such as oxidation and deprotonated/hydride subtracted complicated DAPCI mass spectra in the absence of a charge exchange reagent such as naphthalene.

2.2 Experimental Section

Chemicals and reagents. 1,4-dihydronaphthalene, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthalene, dibenzothiophene, 2,2'-bithiophene, 1,8-dinapthylenethiophene, carbazole, 1,2,3,4-tetrahydrocarbazole, 5-methylcarbazole,n-phenycarbazole, indole, 2-methylindole, quinoline, isoquinoline, aniline, 2,5-dimethylaniline, 1, 2, 3, 4-tetramethylbenzene**,** pentamethylbenzene,

hexamethylbenzene, 2, 6-diphenylpyridine, 3-butylpyridine, 3-phenylpyridine, 9-ethylfluorene, 1-methylfluorene, 9-phenylfluorene, (11H)-benzo-beta-fluorene, hexadecane, docosane, triacontane, icosane, octadecane, and naphthalene-d_8 were purchased from Sigma-Aldrich Inc (Milwaukee, WI, USA), whereas chrysene**,** benzo(ghi)perylene**,** pyrene**,** fluorene**,** phenanthrene**,** fluoranthene and acenaphthylene were obtained from Supelco Analytical (Bellefonte, PA USA). Naphthalene was obtained from Fisher Scientific (Fair Lawn, NJ, USA) and chloroform (HPLC grade) from Mallinckrodt Baker Inc. (Phillipsburg, NJ). Crude petroleum oil samples (API 35 and Arabic light crude oil) samples were donated by BP UK, while the gas/diesel standard mixtures were obtained from Cerilliant Corporation (Round Rock, Texas, USA).

Sample Preparation. Compounds in the liquid phase were used in their pure form without any dilution or sample pre-treatment whereas 3-10 mg of solid samples were dissolved into 10-100 µL of chloroform or methanol and 1-3 µL of each sample was deposited on a filter paper (Grade 1 Whatman, Maidstone, UK) surface for analysis by DAPCI-MS.

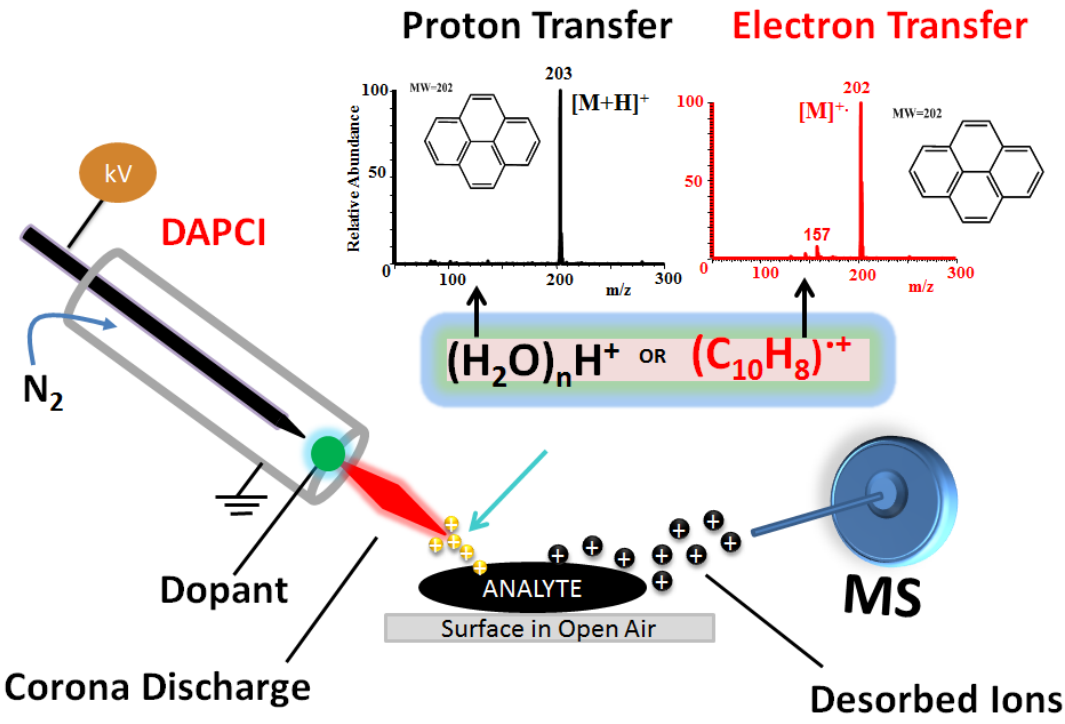


Figure 2.1: Schematic of the DAPCI ion source for analysis of petroleum oil hydrocarbons related compounds from ambient surfaces using two different modes of ionisation (i.e., proton versus electron transfer) under ambient conditions. Naphthalene vapour was doped into the DAPCI carrier gas as the charge exchange reagent for the electron transfer reactions.

Desorption atmospheric pressure chemical ionisation mass spectrometry (DAPCI-MS). The configuration of the DAPCI system used here was identical to that described earlier [17]. It consists of a stainless steel needle with an elongated tapered tip, connected to a high voltage power supply (Figure 2.1). The elongated tip projects from a Teflon capillary tube carrying a high velocity flow of gas. The carrier gas is directed towards a substrate/surface to desorb and ionise analyte(s) which may be present. The carrier gas can be an inert gas such as N_2 or He etc. In all experiments, the voltage applied to the electrode was typically between about ± 3 to 3.5 kV so as to produce a corona discharge in close proximity to the tip of electrode. In some experiments, naphthalene vapour was introduced by placing cotton soaked in a 10 ppm solution of naphthalene in chloroform in the DAPCI source to cause

charge transfer reactions (Figure 2.1). The ion source is coupled to a suitable mass spectrometer simply by placing it near the atmospheric inlet.

Mass Spectrometry Instrumentation. Experiments were done using a Thermo LTQ linear ion trap mass spectrometer (Thermo Scientific San Jose, CA) tuned for optimum detection of the precursor ion of interest in the positive mode. The DAPCI ion source was placed 2-3 mm in front of the MS inlet capillary and set at 45^{o} to the sample surface as shown in Figure 2.1. The potential on the needle was set to ±3.5 to 40 kV to generate a corona discharge that is carried by the nitrogen carrier gas at a flow rate of 1 L/min. Primary ions are generated in the carrier gas by traces of impurities, especially water. The resulting water cluster ions impact the sample surface for desorption/ionisation so that ions of the analyte(s) are created under ambient conditions (as illustrated in Figure 2.1). The analyte(s) ions are then transferred into the LTQ mass analyser for mass analysis via the ion guide system of the instrument. The LTQ mass spectrometer was set to operate in the positive ion mode and the capillary voltage set to 15V, temperature set to 150^{o}C, while the tube lens voltage was set at 65V.

All mass spectra were recorded as peak profiles with averaging time of 1 min and were background subtracted unless otherwise stated in the positive ion mode. MS/MS was performed on the molecular ion signals of interest, isolated using mass windows of 1 – 2 *m/z* units (manufacturers units) and using 15-45 eV collision energy in all experiments.

2. 3. Results and Discussion

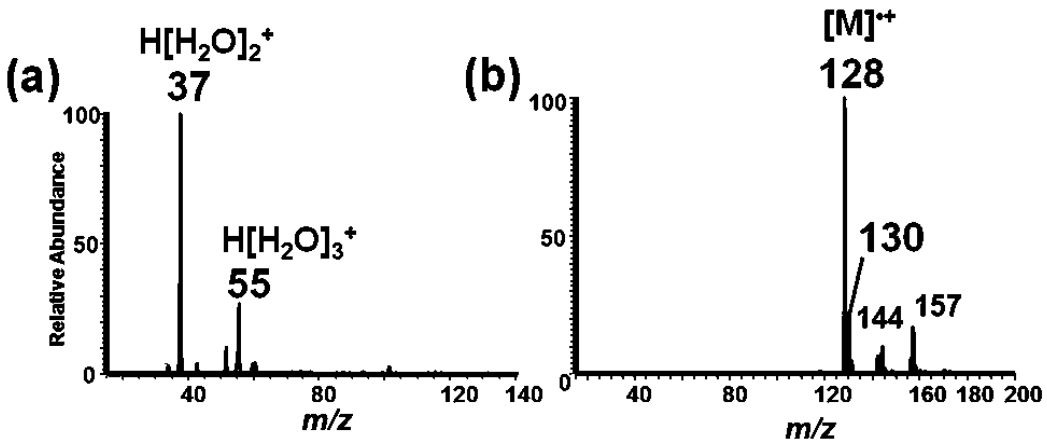


Figure 2.2: Mass spectra showing typical DAPCI background when (a) only nitrogen carrier gas is used and (b) naphthalene is doped into the nitrogen carrier gas.

A typical DAPCI background mass spectrum was first recorded using the normal DAPCI experimental conditions in which only a corona discharge and nitrogen carrier gas are used in the open air (Figure 2.2 a). This mass spectrum shows predominantly the presence of protonated water clusters $H[H_2O]_2^+$ and $H[H_2O]_3^+$ at *m/z* 37 and 55, respectively. Highly volatile solvents in the laboratory environment produce background peaks at *m/z* 33, 42 and 60 corresponding to protonated methanol, acetonitrile, and acetone, respectively. On the other hand, a completely different background spectrum with better signal/noise ratios resulted (Figure 2.2 b) when the headspace vapour of naphthalene (ionisation energy (IE) 8.1 eV, proton affinity (PA) 802.9 kJ mol^{-1}) was doped into the DAPCI gas stream. The spectrum typically showed naphthalene radical cation at *m/z* 128 along with related peaks at *m/z* 130, 144 and 157. By using naphthalene-d_8 as the DAPCI charge exchange reagent, peaks at *m/z* 130 and 144, in the background were confirmed to be related to naphthalene (Figure 2.3). They appear to be due to (i) oxidation, leading to

the addition of atomic oxygen to naphthalene at *m/z* 144 and (ii) reduction of naphthalene to give the ion of *m/z* 130. Careful consideration of the data shows that three different process have been identified to be responsible for these three background ions: (i) oxidation, leading to the addition of atomic oxygen to naphthalene at *m/z* 144, (ii) reduction of naphthalene to give *m/z* 130 ion, and (iii) reduction, followed by substitution of hydrogen atom with ethylene (MW 28); this gives rise to *m/z* 157 peak. In order to confirm these processes, naphthalene-d_8 was introduced at the DAPCI sampling area (Figure 2.3 b). The DAPCI mass spectra recorded from this experiment showed similar pattern as that recorded for naphthalene. Two extra peaks besides the molecular ion (*m/z* 136) of naphthalene-d_8 at *m/z* 152 and 164 were also observed (Figure 2.3 b) Notice how both ions at *m/z* 136 and 152 (Figure. 2.3 b) are shifted by 8 Da from the original values at *m/z* 128 and 144 (Figure 2.3 a) respectively. This strongly suggests that oxidation is a real chemical process which occurs during the analysis of naphthalene and naphthalene-d_8 using DAPCI. Reduction and related processes were also confirmed. For example, CID data from MS^2 and MS^3 product ion spectra of peak at *m/z* 157 via *m/z* 130 ion (Figure 2.3 c and 2.3 d) indicated that the background ions *m/z* 130 and 157 are related. The *m/z* 157 ion was formed from the *m/z* 130 ion through substitution of hydrogen atom by a neutral species having molecular weight 28 Da. In fact, a similar process can account for the ion at *m/z* 164 (Fig 2.3 b) via a substitution of deuterium atom by the same neutral species. Collision-induced dissociation (CID) of an ion at *m/z* 157 predominantly generates *m/z* 130 ion via a loss of acetylene (MW 26 Da) and hydrogen atom, indication that the neutral substituting species is neither CO nor N_2 but rather ethylene. As such we can hypothesise that the *m/z* 130, 144 and 157 background ions typically recorded in blank mass spectra when naphthalene is used

as reagent ion for charge exchange in DAPCI experiments are indeed related to naphthalene itself. The identities of these ions as well as the chemical processes leading to their formation have been elucidated. CID data from MS/MS experiments and the use of naphthalene-d_8 reagents were useful in this investigation.

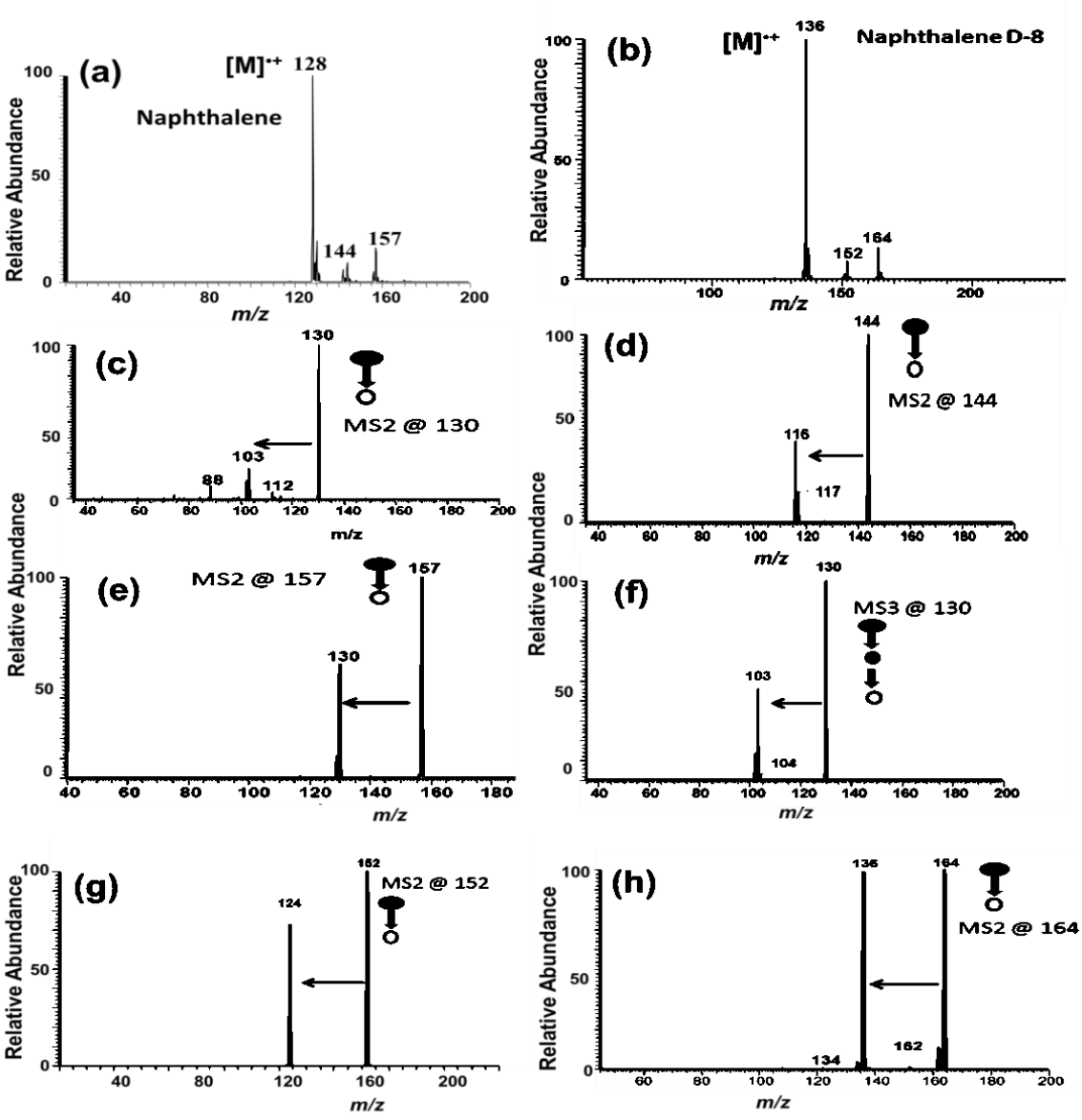


Figure 2.3: Mass spectra showing DAPCI background with; naphthalene, b) naphthalene-D8 dopant. CID MS/MS data of the dominant peaks (c)- (e) at *m/z* 130, 144, 157 respectively, (f) shows the MS/MS/MS for the peak at *m/z* 157 to 130, while (g) and (h) shows the CID MS/MS data for the DAPCI background with naphthalene-D8 at *m/z* 152 and 164 respectively.

Mass spectra recorded using DAPCI under protonating conditions are dominated by the protonated molecules $[M+H]^+$. This reaction is possible under the conditions of the experiment as long as it is exothermic, i.e. the proton affinity (*PA*) of the analyte exceeds that of water (PA_{water} = 697 $kJmol^{-1}$). The mass spectra recorded for 2, 2'-bithiophene (MW 166) and pyrene (MW 202) using DAPCI (Figures 2. 4 a and c) showed protonated molecular ions $[M+H]^+$ at *m/z* 167 and 203 respectively.

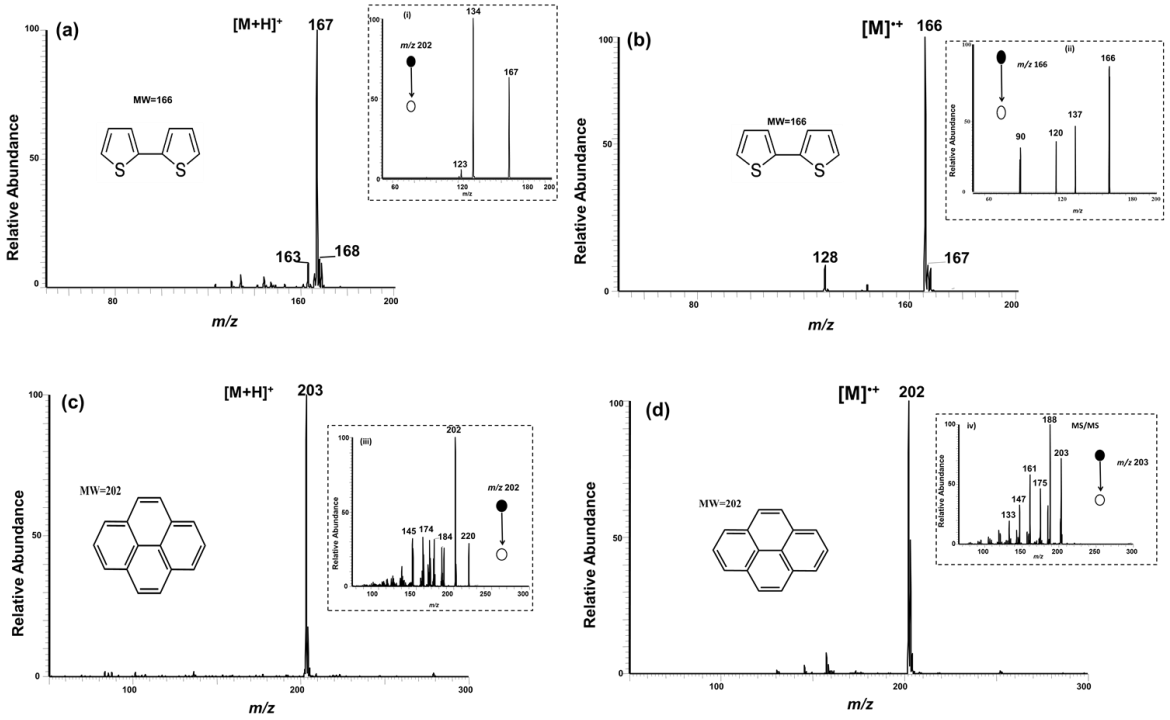


Figure 2.4: DAPCI spectra of 2,2'-bithiophene (a) without naphthalene (b) with naphthalene added as charge exchange reagent, and pyrene (c) without naphthalene d) with naphthalene added as charge exchange reagent.

The identities of these protonated compounds were confirmed through collision-induced dissociation (CID) experiments. Inserts (i)-(ii) shows that dissociation of the 2,2'-bithiophene protonated $[M+H]^+$ molecular and radical cation at *m/z* 167 and 166 respectively, provided a fragment ion at *m/z* 134 via the loss of a

neutral radical -[SH], mass 33 Da. While the CID fragmentation pattern of the pyrene protonated $[M+H]^+$ molecular and radical cation ion at *m/z* 203 and 202 respectively (inserts (iii)-(iv) Figure 2.4), resembles the common fragmentation mechanisms seen for ionic PAHs [i.e., i) formation of $(M-H_n)^+$ ion, ii) ring opening and extensive isomerization leading to CH_3 and $(CH_2)_n$ losses] [32]. However, unlike high energy collision processes, low mass fragment ion series $(C_nH_2)^+$ and $C_nH_3^+$ are not observed. When the same compounds were analysed in the presence of naphthalene, radical molecular cations were observed in the mass spectrum for both 2,2'-bithiophene (MW 166) and pyrene (MW 202) (Figure 2.4 b and d). Radical molecular cations of these analyte(s) were generated via an electron transfer reaction with naphthalene radical cations $M^{+\bullet}$. Again, this charge exchange process is possible as long the ionisation energy of the analyte(s) is lower than that of naphthalene. A complete list of petroleum constituents analysed under these two different ionisation conditions (proton vs. electron transfer) is provided in Table 2.1. As can be seen, the majority of the analyte(s) investigated have proton affinities higher than that of the water cluster ions and so allow proton transfer reactions to yield protonated molecules $[M+H]^+$ under ambient conditions, as is observed for the pyrene and 2,2'-bithiophene model compounds (Figure 2.4 a and c). Again electron transfer or charge exchange can take place if the ionisation energy of the analyte(s) of interest is lower than the ionisation energy of the reagent (naphthalene). For example, two of the hydronaphthalene species (Table 2.1, entries 1and 3) could be ionised by naphthalene reagent but 1, 2, 3, 4-tetrahydronaphthalene could not. This is simply because the ionisation energy of 1, 2, 3, 4-tetrahydronaphthalene is higher than that of naphthalene, making the electron transfer reaction endothermic.

The charge exchange reaction using naphthalene was particularly interesting in that; (i) it provides a simpler mass spectrum with higher abundance molecular radical cations compared with proton transfer, (ii) it served as a complementary technique in which prior information obtained about a analyte can be confirmed via generation of a different ionised form, and (iii) it extends the applicability of DAPCI to hydrocarbons that could not be ionised by proton attachment. An example of this extension is the high molecular weight PAH chrysene. As shown Table 2.1, molecular radical cations were generated from all analyte(s) tested (provided the thermochemistry permits) with no unwanted side reaction when naphthalene was doped into the DAPCI gas stream. Unfortunately, side reactions were observed during the normal protonation DAPCI mode in which the corona discharge is pneumatically directed at the sample using nitrogen as carrier gas. Besides protonation, other reactions such as hydride abstraction and oxidation of analyte(s) were observed under these normal DAPCI experimental conditions (e.g., entries 6, 7, 13, and 14, Table 2.1).

Other model compounds such as fluorenes, hydronaphthalenes and low molecular weight n-alkanes were among the tested petroleum constituents that gave rise to $[M-H]^+$ forms of the molecules molecular ion species though hydride abstraction (Figure 2.5 and Table 2.1). Such behaviour is characteristic of the gas-phase ion/molecule reactions of molecules of low proton affinity and is also observed in chemical ionisation and plasma desorption/ionisation methods. The formation of $[M-H]^+$ ions in plasma-based ionisation methods has been attributed to possible gas-phase "self" chemical ionisation [23]. Hydride abstraction or deprotonating $[M-H]^+$ can also be formed due to reactions of such ionic species as NO^+ in the plasma with the analyte(s) [24]. No such reagents were found in the

DAPCI background and so the presence of $[M-H]^+$ ions can be attributed to self-chemical ionisation. In this reaction, molecular radical cations of the analyte react with neutral analytes via hydride – or equivalently hydrogen atom - abstraction, neutralizing the radical cation and forming deprotonated molecules $[M-H]^+$. This reaction is governed by the fact that the heat of formation of radical cations is usually higher than the heat of formation of the corresponding deprotonated molecular ion species $[M-H]^+$ species [24]. However, this depends on the specific chemical properties of the analyte(s) as well as the experimental conditions. The presence of $[M-H]^+$ ions also requires that the proton affinity (PA) of the analyte(s) [M] is lower than that of the corresponding dehydrogenated molecule [M-2H]. As can be seen in Table 2.1, $[M-H]^+$ molecular ion species cannot be generated for molecules without saturated secondary/tertiary carbon. This ion was also not observed for any of the nitrogen containing molecules whose PA is too high to allow the formation of $[M-H]^+$ ions.

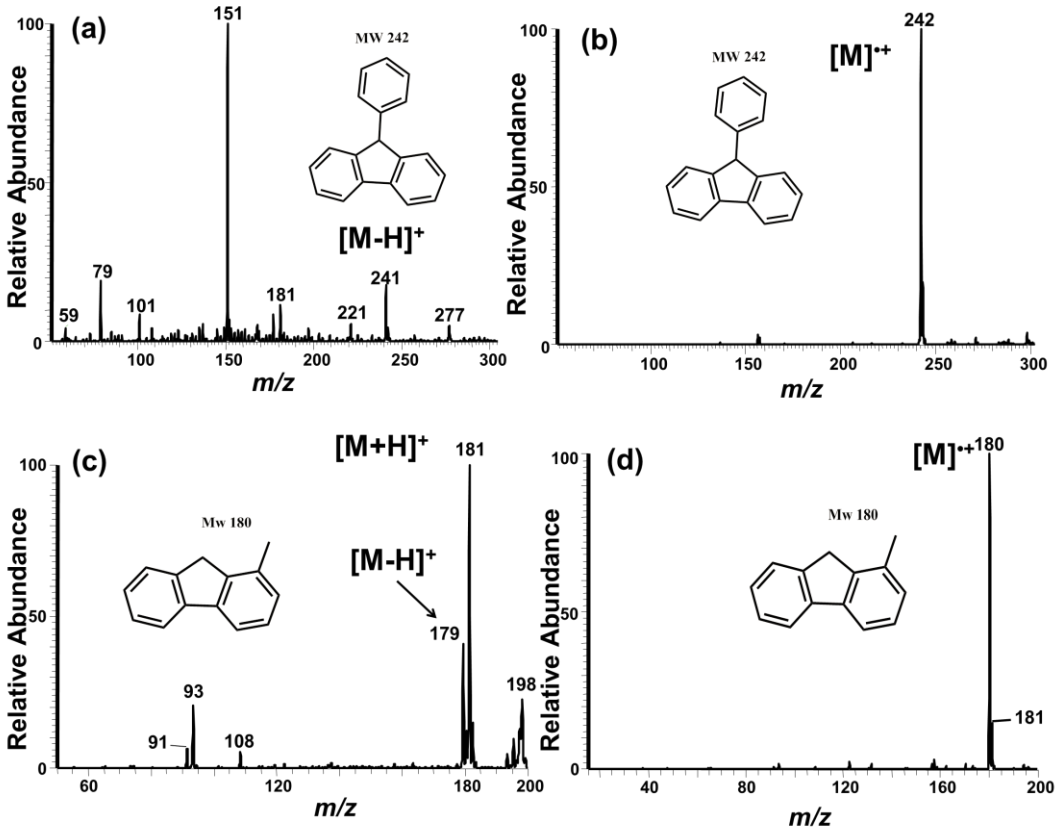


Figure 2.5: Mass spectra of (11H)-benzo-β-fluorene (M) analysed (a) without naphthalene b) analysed with naphthalene added as charge exchange reagent, c) 1-methylfluorene without naphthalene d) 1-methylfluorene with naphthalene added as charge exchange reagent.

Excessive fragmentation was observed for all *n*-alkanes tested with the $[M-H]^+$ ion being completely absent or present only in small quantities. Interestingly, no fragmentation was observed for other analytes such as the fluorenes and the hydronaphthalenes. Intact protonated molecules were observed for these two class of compounds in addition to the $[M-H]^+$ ions (Figure 2. 5 (a) and (c)). It is also important to note that only a single ionisation mechanism was observed when naphthalene was doped into the DAPCI gas stream. In other words, only the radical cations were observed in the presence of a charge exchange reagent such as naphthalene (Figure 2. 5 b and d).

Just as most tested compounds yielded only the radical molecular cations upon interaction with naphthalene radical cations, so did the substituted alkylbenzenes (Figure 2.6 (b) and (d)). On the other hand, analysis of tetramethylbenzene and pentamethylbenzene using the normal protonating mode DAPCI (viz. in the absence of naphthalene) sometimes produced $[M+O]^{+\bullet}$ ions in addition to the $[M+H]^{+}$. For example, analysis of pentamethylbenzene (MW 148) using DAPCI under the conditions associated with protonation provided peaks at *m/z* 147, 149 and 163, which correspond to $[M-H]^{+}$, $[M+H]^{+}$ and $[(M-H)+O]^{+\bullet}$, respectively. Peak identities were confirmed by tandem-MS experiments (MS/MS). The oxidation reaction was a surprise, but was observed also for tetramethylbenzene although not for hexamethylbenzene. Although not fully understood there is precedent for oxidation in both DESI [25] and LTP [26] ambient ionisation experiments and there is evidence that production of ozone is responsible in at least some cases.

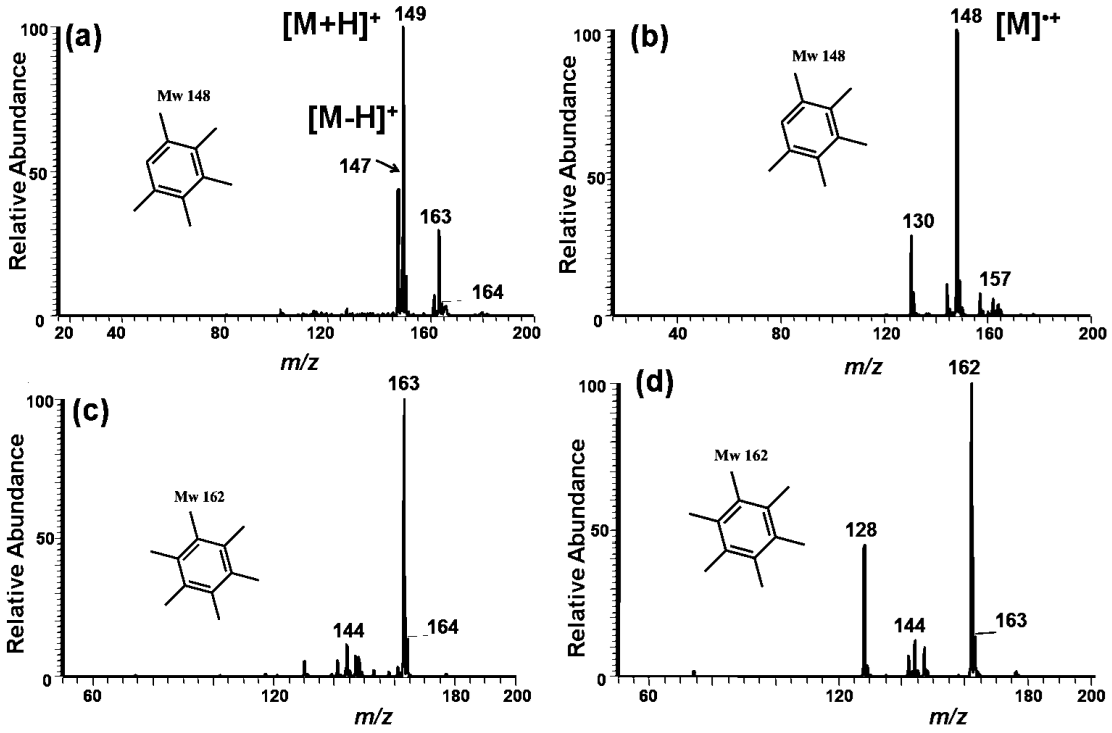


Figure 2.6: Mass spectra of a) pentamethylbezene without adding naphthalene as charge exchange reagent b) pentamethylbezene with naphthalene c) hexamethylbenzene without naphthalene as charge exchange reagent d) hexamethylbenzene with naphthalene.

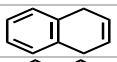
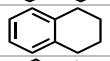
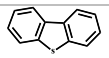
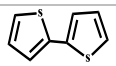
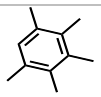
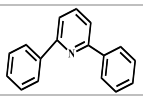
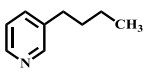
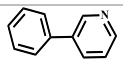
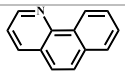
Many nitrogen-containing compounds are widely used on a large scale as chemical feed stock within the chemical industry [27]. Nitrogen-containing compounds such as the primary aromatic amines have either a proven or suspected carcinogenic nature and are rated as highly toxic [28-31], which have led to strict regulation in cosmetic products [32]. |Despite the chemical carcinogenic and toxic nature of the nitrogen compounds [33], nevertheless they are still used in the chemical manufacturing industry as feedstock in the formulation of pharmaceuticals, pesticides, explosives, polymers, aromatic polyurethane products and dyes. While not desirable the presence of their residues in the final products may be due to the incomplete reactions (e.g. by (degradation or by-products). For instance nitrogen-containing compounds can be found in organic dyes as impurities. Organic dyes are used extensively on a large scale worldwide as: printing inks, paints, textiles,

cosmetic and personal care products, plastics used to make food packaging materials [34, 35]. As such, in order to safe-guard public safety and product efficacy, the cosmetics and personal care industry is highly regulated. Therefore, manufacturers who use nitrogen compounds in their formulations must monitor and quantify various regulated limitations, such as the presence of nitrogen-containing compounds.

Just as other model compounds were analysed as discussed above, nitrogen-containing compounds were also studied using the DAPCI ionisation method that favours proton transfer due to their higher proton affinities [36-38]. The identification and structure characterization of nitrogen-containing compounds is also paramount to the petroleum industry before and after the refining processes such (e.g. desulfurization and hydrogenation) [39, 40]. Four different groups of nitrogenous species (carbazole, indole, quinolines and aniline) were selected for study using DAPCI mass spectrometry. A typical background mass spectrum was first obtained before sample analysis using the DAPCI mass spectrometry in which only a corona discharge and nitrogen carrier gas are used (Figure 2.2 a).

The Mass spectra obtained for all the nitrogen-compounds (i.e. carbazole, indole, quinolines, and aniline) analysed with DAPCI under protonating conditions are dominated by the protonated ion molecules $[M+H]^+$ (Figure 2.7 a). The identities of these protonated compounds were confirmed through collision-induced dissociation (CID) experiments. For instance insert (i) (Figure 2.7 b) shows the dissociation of the intact 5-methylcarbazole protonated molecule at *m/z* 182 gives a single fragment at *m/z* 167 due to loss of a neutral methyl [$-CH_3$], (MW 15). The stability of the CID signal obtained and abundance of such product ions allowed a three-stage tandem mass spectrometry (MS/MS/MS) experiment and in this case

CID[3] or MS/MS/MS of the product ion at *m/z* 167 yielded fragment ions at *m/z* 139 (major) and *m/z* 140 (minor) through sequential losses of [-28 Da] and [-27 Da] (insert (ii) Figure 2.7 b). Such multiple stage MS experiments allow definitive confirmation of the identity of the analyte(s).

	Compound name	Structure	IE (eV)	PA kJ mol^{-1}	MW	Species detected	
						Without naphthalene	**With naphthalene**
Hydronaphthalenes							
1	1,4-dihydronaphthalene		7.9[d]	879[c]	130	$[M+H]^+$	**$[M]^{\bullet+}$**
2	1,2,3,4-tetrahydronaphthalene		8.5[a]	809.7[b]	132	$[M-H]^+$	**Notdetected**
3	1,2-dihydronaphthalene		8.1[a]	859[c]	130	$[M-H]^+$ $[M]^{\bullet+}$	$[M]^{\bullet+}$
Thiophenes							
4	Dibenzothiophene		7.9[f]	815[h]	184	$[M+H]^+$	$[M]^{\bullet+}$
5	2,2'-bithiophene		7.8[g]	859[e]	166	$[M+H]^+$	**$[M]^{\bullet+}$**
Alkyl substituted benzenes							
6	1,2,3,4-tetramethylbenzene		8.1[i]	840[j]	134	$[M+H]^+$ $[(M-H)+O]^+$	**$[M]^{\bullet+}$**
7	Pentamethylbenzene		7.9[k]	850.7[l]	148	$[M+H]^+$ $[M-H]^+$ $[(M-H)+O]^+$	**$[M]^{\bullet+}$**
8	Hexamethylbenzene		7.9[m]	860.6[n]	162	$[M+H]^+$	**$[M]^{\bullet+}$**
Pyridines							
9	2,6-diphenylpyridine		*	*	231	$[M+H]^+$	**$[M+H]^+$**
10	3-butylpyridine		8.5[o]	960[p]	135	$[M+H]^+$	**$[M+H]^+$**
11	4-tert-butylpyridine		*	*	135	$[M+H]^+$	**$[M+H]^+$**
11	3-phenylpyridine		*	940[q]	155	$[M+H]^+$	**$[M+H]^+$**
12	7,8-benzoquinone		8.3	*	179	$[M+H]^+$	**$[M+H]^+$**
Fluorenes							
13	9-ethylfluorene		7.5[r]	850[s]	194	$[M-H]^+$ $[M+H]^+$	**$[M]^{\bullet+}$**

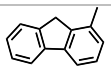
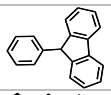
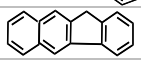
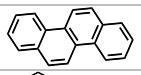
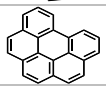
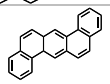
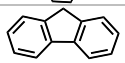
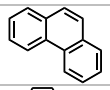
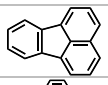
14	1-methylfluorene		7.5[t]	860[u]	180	$[M-H]^+$ $[M+H]^+$	$[M]^{\bullet+}$
15	9-phenylfluorene		7.1[v]	820[w]	242	$[M-H]^+$	$[M]^{\bullet+}$
16	(11H)-benzo-beta-fluorene		6.4[x]	880[y]	216	$[M+H]^+$	$[M]^{\bullet+}$
Polycyclic Hydrocarbons (PAH)							
17	Chrysene		7.6[ac]	840[ab]		Not detected	$[M]^{\bullet+}$
18	Benzo(ghi)perylene		7.1[ad]	876[ab]	276	$[M+H]^+$	$[M]^{\bullet+}$
19	Dibenz(a,h)anthracene		7.4[ae]	*	276	$[M+H]^+$	**Not detected**
20	Pyrene		7.4[af]	869[ab]	202	$[M+H]^+$	$[M+H]^+$, $[M]^{\bullet+}$
21	Fluorene		7.9[ag]	831[ab]	166	$[M+H]^+$	$[M+H]^+$
22	Phenanthrene		7.9[ah]	825.7[ab]	178	$[M+H]^+$	$[M]^{\bullet+}$
23	Fluoranthene		7.9[ai]	829[ab]	202	$M+H]^+$	$[M]^{\bullet+}$
24	Acenaphthylene		8.2[ak]	206[ij]	152	$[M]^{\bullet+}$	$[M]^{\bullet+}$

Table 2.1: Hydrocarbons and related compounds analysed by DAPCI and their thermochemistry.

IE = Ionisation Energy

PA = Proton Affinity (the enthalpy change upon protonation or the GB = Gas-phase basicities (the Gibbs free-energy change upon protonation)

Mw = Molecular Weight

$[M+H]^+$ = Protonated molecular ion species

$[M]^{\bullet+}$ = Radical molecular cation species

lFrom Ref.[41, 42], [a]From Ref. [43], [b]From Ref.[41], [c]Estimated using vinyl benzene and 1,2,3,4-tetrahydronaphalene proton affinities,[d]Estimated using allylbenzene and 1,2,3,4-tetrahydronaphthalene ionisation energies, [e]Estimated using methylthiophene data, [h]Estimated using thiophene (thiophene has higher PA than benzene), [g]From Ref.[44], [f]From Ref. [44], [i]From Ref.[45], [j]Estimated from proton affinities of pentamethylbenzene and hexamethylbenzene, [k]From Ref.[45], [m]From Ref. [45], [n]From Ref. [41], [o]Estimated using 3-methylpyridine and 3-ethylpyridine ionisation energies, [p]Estimated from PA's of 3-methylpyridine and 3-ethylpyridine, [q]Estimated using 4-phenylpyridine PA, [r]Estimated using EI of fluorene and ethylfluorene, [s]Estimated using PA's of fluorene and ethylfluorene, [t]Estimated as IE (fluorine) – IE(benzene – toluene), [u]Estimated as PA (fluorine) – PA (benzene – toluene), [v]Estimated as IE(ethylfluorene) + IE (benzene – toluene)],[w]Estimated as PA(ethylfluorene) + PA(phenylamine – ethylamine)], [x]Estimated as IE(fluorine) + IE(naphthalene – benzene), [y]Estimated as PA(fluorine) + PA(naphthalene – benzene), [A]From Ref. [46], [B]From Ref. [47].[C]From Ref. [42], [D]From Ref. [48], [E]From Ref. [49], [F]From Ref. [42], [G]From Ref. [50], [H]From Ref. [51], [I]From Ref. [41], [J]From Ref.[41], [*]Not available.

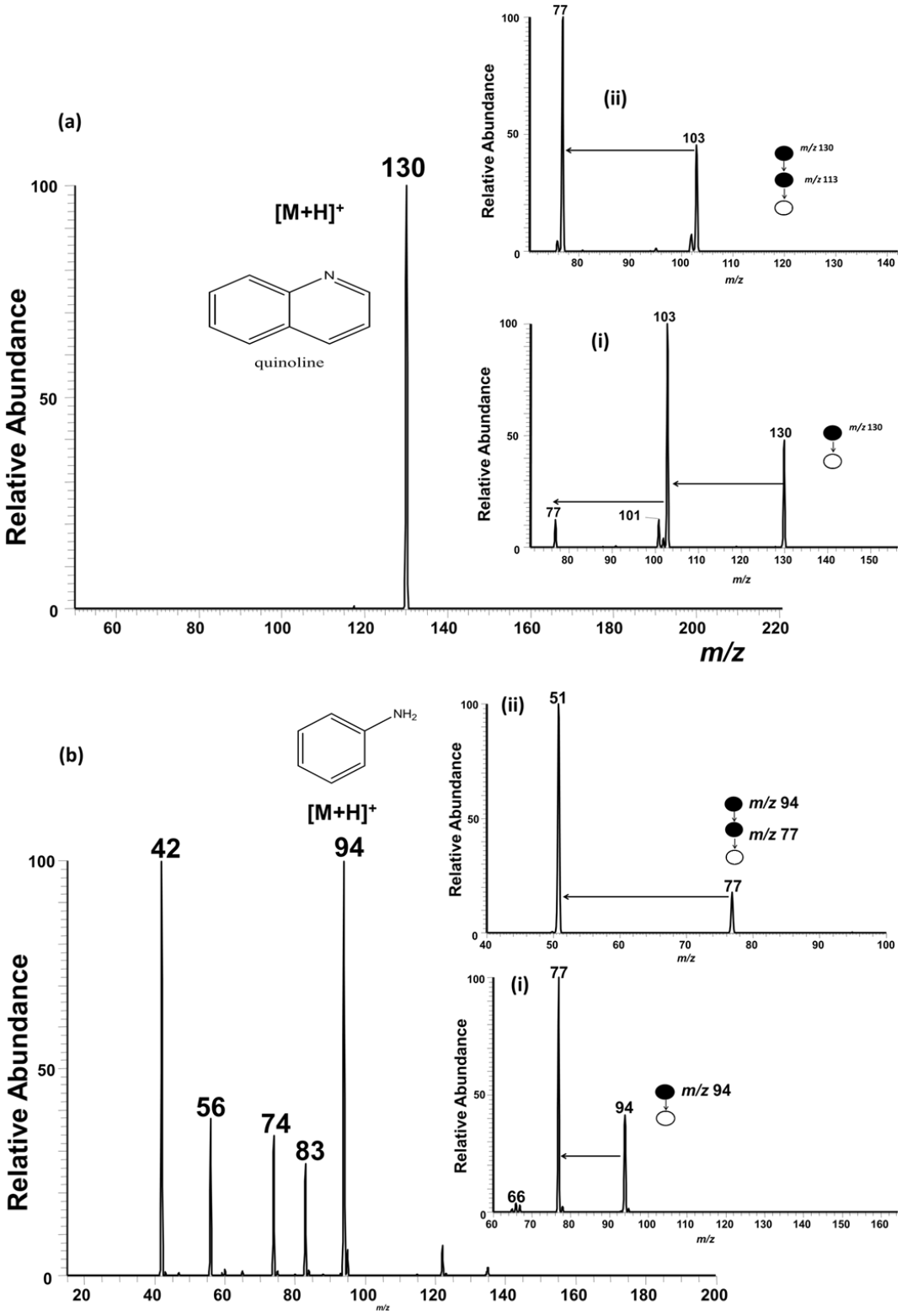


Figure 2.7: Positive DAPCI CID MS/MS spectra of non-basic nitrogen-containing compounds: (a) indole, and (b) 5-methylcarbazole three stage experiment MS^3.

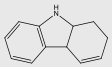
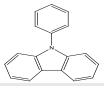
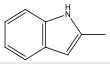
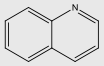
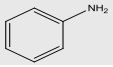
Name	Structure	Mw	$[M+H]^+$	MS/MS	MS/MS/MS
Carbazole		167	168	168→139- [29]	168 → 139→113
1,2,3,4-tetrahydrocarbazole		170	172	172→130 -[42]	172 → 130→ 103
5-methylcarbazole		181	182	182→162-[15 or CH_3]	182 → 162→ 139
N-phenycarbazole		244	244	244→166-[78 or C_6H_6]	244 →166 → 139
Indole		118	118	118 →91-[27 or HCN]	118 → 91 → 65
2-methylindole		131	132	132→117 -[15 or CH_3]	132→ 117 → 90
Quinoline		129	130	130 →103 -[27 or HCN]	130 → 103→77
Isoquinoline		130	130	130 →103-[27 or HCN]	130 → 103→77
Aniline		93	94	94 → 77-[17 or NH_3]	94 → 77→51
2,5-dimethylaniline		121	122	122 →107-[15 or CH_3]	122 → 107→76

Table 2.2: List of the different nitrogen containing model compounds analysed by DAPCI-MS.

Mw = Molecular Structure
$[M+H]^+$ = Protonated molecular ion species
MS/MS = Two stage tandem mass spectrometry
MS/MS/MS=Three stage mass spectrometry

2.3.1 Mixture Analysis using DAPCI-MS

The ability to analyse hydrocarbons in mixtures using DAPCI-MS was investigated. First an artificial mixture was made by mixing equal volume of the nitrogen-containing model compounds (i.e. carbazole, 1,2,3,4-tetrahydrocarbazole, 5-methylcarbazole, *N*-phenycarbozole, indole, 2-methylindole, quinoline, isoquinoline, 8-methylquinoline, 7,8-benzoquinoline, dibenzoquinoline, aniline, 2,5-

dimethylaniline in acetonitrile solvent to form a mixture of nitrogen compounds at 100 ppm. The stock solution of nitrogen compounds was then mixed in the vacuum pump oil to mimic the petroleum crude oil sample matrix. Approximately 3 ng/µL of each compound (mixed in 1µL of acetonitrile) was deposited onto a paper substrate and analysed using a commercial benchtop mass spectrometer in positive ion mode under the protonating DAPCI conditions Figure 2.1 without a dopant. The resulting typical mass spectrum obtained is shown in Figure 2.8. The mass spectra showed a relatively stable signal of protonated molecules generated under ambient conditions without any sample preparation. Again each of the individual components can be identified and be characterized by MS/MS (Figure 2.7 (see Table 1 for details). The model compound mixture of the nitrogen compounds gave relatively stable signal with DAPCI ambient ionisation and produced no observable fragmentation in the full mass spectrum. Also the relative signal intensities from the artificial mixtures did not correspond to the concentration of each component in the mixture due to ion suppression from other components. Aniline, quinolone, carbazole and indole model compounds were readily observed in the full MS scan (Figure. 2.8) and their identities confirmed using MS/MS experiments.

Under the DAPCI experimental conditions favouring protonation (i.e. without dopants), water clusters $[H_3O]_n^+$ or hydronium ions are formed in the DAPCI in the open air (Figure 2.1). When DAPCI is operated under ambient conditions (Figure 1a) water molecule(s) are ionised by interacting with the corona discharge at the sampling area. Due to this ion molecule reaction, high abundant water cluster ions $H[H_2O]_2^+$ and $H[H_2O]_3^+$ ions are observed at *m/z* 37 and 55 respectively. Thus, once these water clusters are ionised, they serve as the primary reactant ions in the DAPCI ionisation process under the conditions in Figure 1 to

yield protonated molecular $[M+H]^+$ ion species as follows (Equation 2.1). As such compounds which have proton affinities higher than the protonated water clusters $[H_3O]_n^+$ (above 688.8 KJ mole $^{-1}$ at room temperature) [52], are ionised by transfer of a hydrogen ion from the water clusters $H[H_2O]_n^+$ ions to the more basic compound [M].

$$\mathbf{[H_3O]_n^+ + [M] \rightarrow [M+H]^+ + nH_2O} \qquad \textbf{(Equation 2.1)}$$

For compounds which have proton affinities lower than that of the hydronium ion $[H_3O]_n^+$ (below 688.8 KJ mol^{-1} at room temperature), transfer of a hydrogen ion from the $[H_3O]_n^+$ or hydronium ions will be endothermic and thus extremely slow or difficult.

Nitrogen-containing compounds have proton affinities in the range of 205-240 kcal mole $^{-1}$ and other hydrocarbons such as alkanes, alkenes, cycloalkanes and substituted benzenes in the range of 150-200 kcal mole $^{-1}$. This difference in proton affinities permits the selective detection of nitrogen compounds in a hydrocarbon matrix (equation 1). From Figure 2.7, it is clear that the higher selectivity of detection for nitrogen-containing compounds is observed using the DAPCI under ambient conditions without the use of a dopant (Figure 2.1). For example hydrocarbon components such as: alkanes, alkenes, cycloalkanes and substituted benzenes in the petroleum oil sample matrix are not ionised and detected, and they do not interfere with the ionisation of the nitrogen compounds in the mixture.

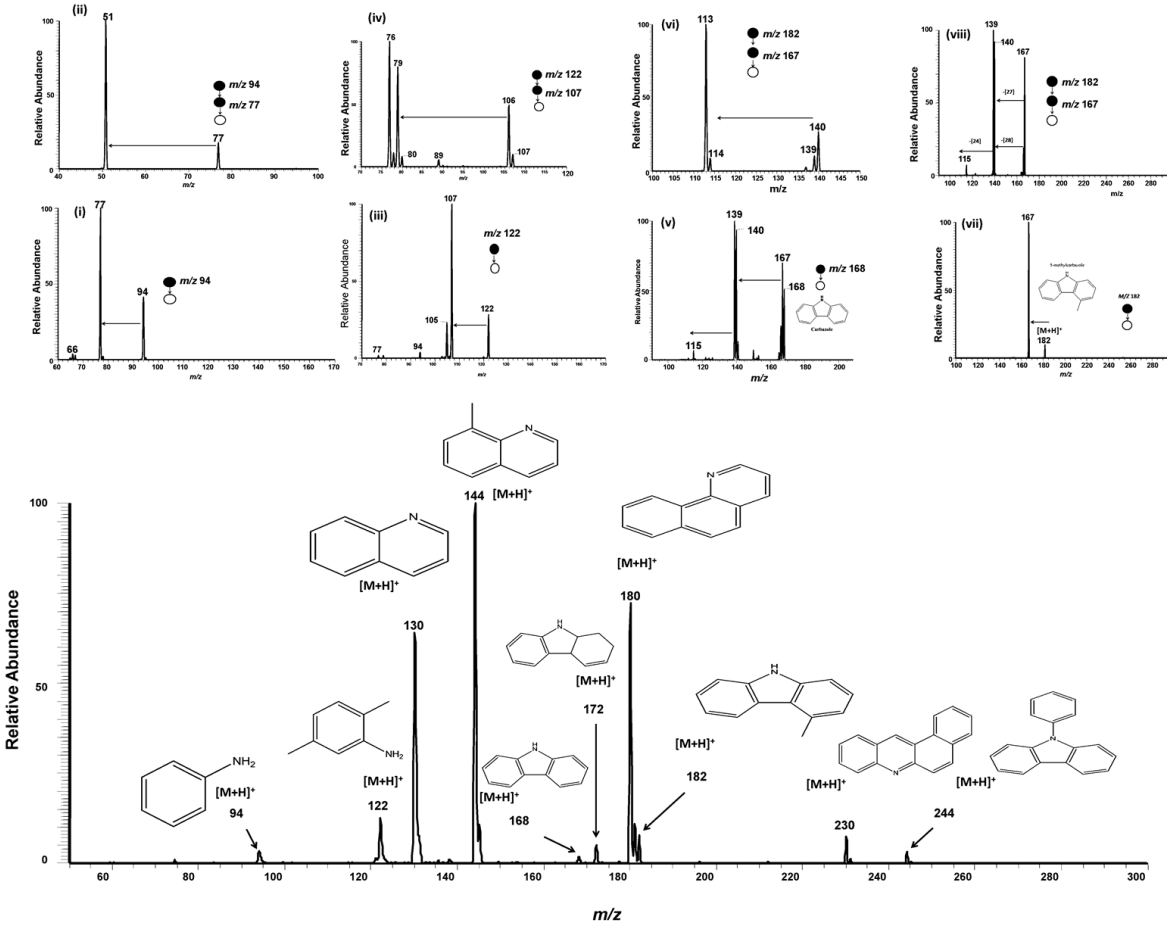


Figure 2.8**:** Positive DAPCI-MS analysis of the nitrogen-containing model compounds mixture of : Carbazole $[M+H]^+$ at *m/z* 168, 1,2,3,4-tetrahydrocarbazole $[M+H]^+$ at *m/z* 172, 5-methylcarbazole $[M+H]^+$ at *m/z* 182, N-phenycarbozole $[M+H]^+$ at *m/z* 244, Indole $[M+H]^+$ at *m/z* 118, 2-methylindole $[M+H]^+$ at *m/z* 132, Quinoline $[M+H]^+$ at *m/z* 130, Isoquinoline $[M+H]^+$ at *m/z* 130, 8-methylquinoline $[M+H]^+$ at *m/z* 144, 7,8-benzoquinoline $[M+H]^+$ at *m/z* 180, Dibenzoquinoline $[M+H]^+$ at *m/z* 230 , Aniline $[M+H]^+$ at *m/z* 94, 2,5-dimethylaniline $[M+H]^+$ at *m/z* 122, and 2,4,6-trimethylaniline, $[M+H]^+$ at *m/z* 135 model compounds mixture in a vacuum pump oil matrix.

The DAPCI-MS experiment was also utilised to analyse a mixture of fluorene model compounds under the proton transfer and electron transfer conditions described above (e.g., as used to acquire the data shown in Figures 2. 2 (a) and 2. 2 (b)). Mass spectra associated with both sets of conditions are shown in Figure 2. 9 a and b, only protonated molecules are generated from the mixture under proton

transfer conditions, while electron transfer conditions provided molecular radical cations.

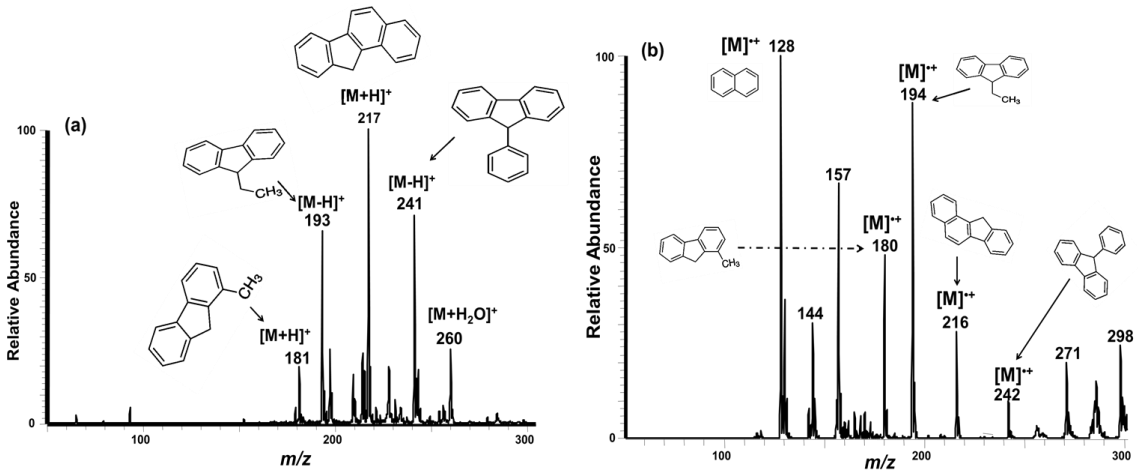


Figure 2.9**:** DAPCI-MS analysis of a mixture of fluorene model compounds ionised (a) without adding naphthalene as charge exchange reagent and (b) with naphthalene.

The DAPCI ion source was also applied to the direct analysis of two types of petroleum crude oil (i.e. API 35 and Arabic light crude oil (Figure 2.10 a-d)) and gas/diesel standard mixtures (of unleaded gasoline and diesel fuels (Figure 2.10 e and f)) in positive ion mode (Figure 2.10). Both the crude petroleum oil and the fuel standards were analysed using two different carrier gas temperatures under normal conditions as well as with naphthalene. Both temperature and reagent have an effect on the data. At higher carrier gas temperature and in the presence of naphthalene (Figure 2.10 a, c and f) higher molecular weight compounds give intact molecular radical cations that dominate the spectrum for both API 35 and Arabic light crude oil as well as the for the fuel standards. While under normal operating temperatures and normal conditions (viz. without naphthalene, Figure 2.9 b, d and f), low molecular weight aromatics components of the diesel standard dominated the spectrum. The full CID MS/MS data are shown in the appendixes A.1-A.8 (Appendix A). These

data are consistent with the two-step desorption/ionisation sequence discussed in the introduction.

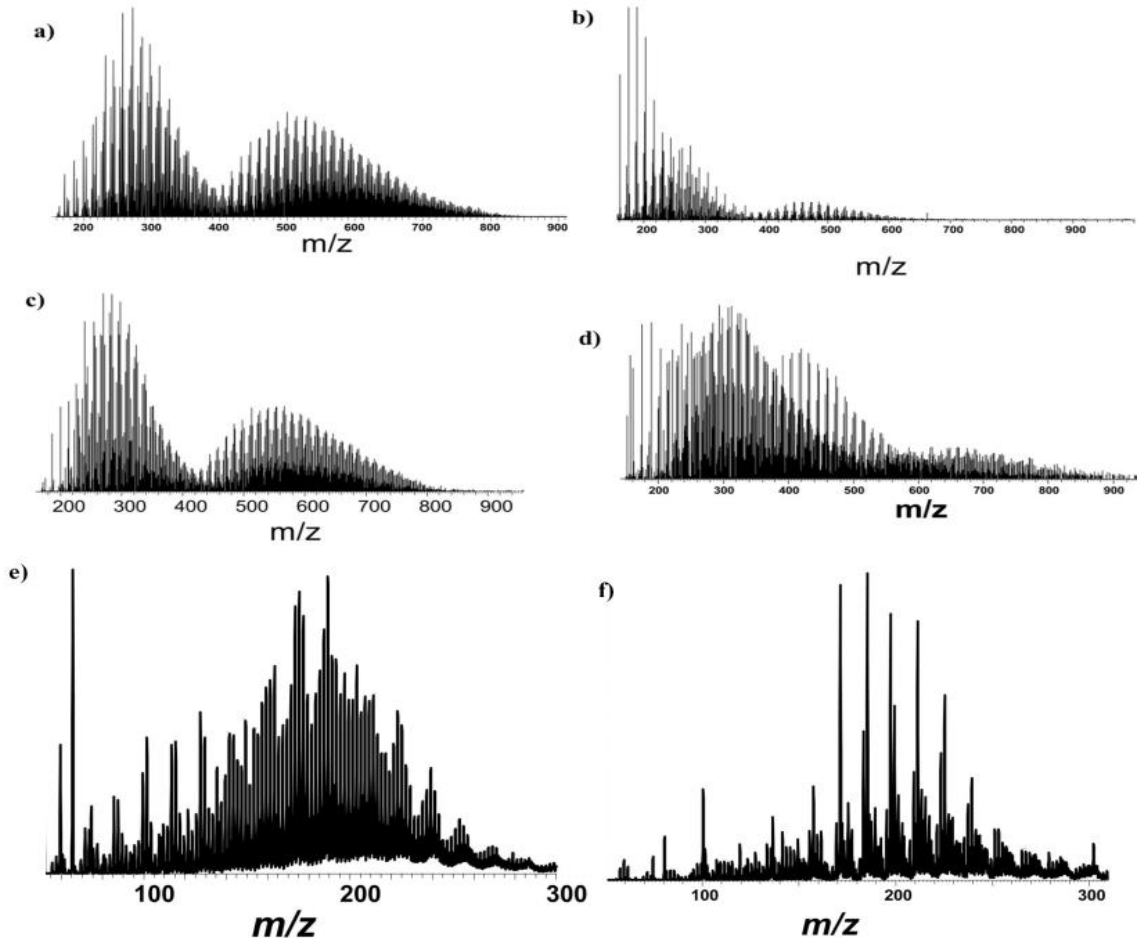


Figure 2.10**:** DAPCI-MS analysis of the crude oil petroleum oil samples with nitrogen carrier gas at 100^{o}C; a) API 35 crude oil with naphthalene, b) API 35 analysed without naphthalene **c)** Arabian light crude oil with naphthalene, Arabian light crude petroleum oil without naphthalene.

2.4.0. Conclusions

This chapter demonstrates the feasibility of using desorption DAPCI-MS for direct *in-situ* analysis of different analyte(s) in open air with little or no sample preparation, using procedures that either favour proton or electron transfers reactions at atmospheric pressure. Both complex petroleum crude oil and fuels (unleaded gasoline and diesel standard) mixtures have also been characterized. DAPCI was found to be especially sensitive for PAHs, and for those petroleum components

containing hetero-atoms (e.g. thiophene and, nitrogen-containing compounds (aniline, indole, quinolone and carbozole), alkylmethyl benzene and pyridine derivatives). Low molecular analyte(s) (<1000 Da) of all functional types were generally successfully ionised. In contrast, DAPCI was found to be transparent to higher molecular weight n-alkanes (saturated hydrocarbons) which could be advantageous in examining petroleum for minor constituents.

The occurrence of proton or electron transfer was found to be highly dependent upon the ionisation conditions. Electron transfer reactions typically gave simpler and less cluttered spectra, producing mainly the molecular radical cations. In contrast, some unwanted reactions associated with proton transfer like self-chemical ionisation that leads to hydride abstraction were observed, as well as oxidation reactions with some functional groups. Subsequent work in this area will involve accurate measurement of sulphur and nitrogen speciation in crude oil and middle distillate, aromatic heterocyclic, polycyclic and fluorinated hetero compounds. In comparison with electrospray based methods like (DESI), DAPCI works well for non-polar compounds and nitrogen containing compounds. While discharge-induced oxidation in desorption electrospray ionisation and derivatisation could help ionisation mainly for unsaturated hydrocarbon in DESI but it is still for unsaturated hydrocarbons [36].

The simplicity of the DAPCI ion source makes it attractive when coupled to a miniature MS for *in-situ* analysis. It could then provide a suitable hand-held, in-field tool for the analysis of heteroatom class petroleum compounds. In this way, DAPCI might be useful for *in-situ* monitoring of important constituents such as thiophenes and nitrogen compounds since no sample preparation is required. The combination

of the DAPCI ion source with a miniaturised portable mass spectrometer for the analysis of PAHs is presented in the next chapter 3 that follows.

2.5.0. References

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Chapter 3 : *In-situ* PAHs Detection Using DAPCI Coupled to a Portable Mass Spectrometer

3. 0 Overview

A desorption atmospheric pressure chemical ionisation (DAPCI) ion source is coupled to a portable/miniature ion trap mass spectrometer (Mini 10), and utilised in the *in-situ* detection of poly aromatic hydrocarbons (PAHs) and alkyl substituted benzenes (i.e. 1,2,3,5-tetramethylbenzene, pentamethylbenzene, hexamethylbenzene, fluoranthene, anthrancene, benzo[*k*]fluoranthene, dibenz[*a,h*]anthracene, acenaphthene, indeno[1,2,3-c,d]pyrene, 9-ethylfluorene, and 1-benzyl-3-methyl-naphthalene). Their identities are confirmed using tandem mass spectrometry (MS/MS) from ambient surfaces in the open air. The presence of these compounds in the environment poses a significant threat to the health of both humans and wildlife due to their carcinogenic, toxic, and mutagenic properties. As such, instant detection outside of the laboratory is of particular importance to allow *in-situ* measurement at the source. This method can provide rapid instantaneous information while minimizing sample preparation, which is advantageous in terms of both cost and simplicity of analysis. This MS-based technique is applicable to a wide range of environmental organic molecules.

3.1 Introduction

The presence of polycyclic hydrocarbons (PAH) in our environment, even at low concentration poses significant health hazards both to humans and wildlife. The PAHs are known to be toxic [1], carcinogenic [2-4], as well as mutagenic [5]. Analytical methods that are capable of monitoring and identifying such hazardous compounds are therefore highly desirable [6,7]. *Ex-situ* methods based on solid phase extraction [8,9] followed by gas chromatography (GC) or liquid chromatography (LC) mass spectrometry (MS) [10-14] are the most widely adopted methods for both quantitative and qualitative analysis of PAHs. Although, high sensitivity and specificity can be achieved using these GC/LC-MS-based methods considerable time is required for sample pre-concentration and pre-treatment, the sample must also be transported to the laboratory for analysis [15-18]. Ambient ionisation methods [19-23] are well suited for portable mass spectrometers [24-27] as vacuum requirements are reduced. Moreover, the flexibility to use different ambient ionisation sources allows a wide range of analyte(s) to be measured *in-situ*.

Ambient ionisation MS is a technique in which ionisation is performed directly on unmodified samples in the air outside the vacuum, and is capable of providing instantaneous data while minimizing sample preparation [28]. In the past 10 years, several ambient ionisation techniques have been exploited in the analysis of environmental organic molecules; most notably desorption electrospray ionisation (DESI) [29, 30], direct analysis in real time (DART) [31,32], low temperature plasma (LTP) [33,34], and paper spray ionisation [35-37]. Desorption atmospheric pressure chemical ionisation (DAPCI) is a plasma-based ambient ionisation source that is relatively underutilized compared to others [38]. DAPCI has been successfully

utilized in the analysis of complex molecules [39] including melamine in powdered milk [40], discriminating between different variants of Chinese tea [41], analysis of fuels and petroleum oil mixtures [42], explosives, and narcotics [43].

In this chapter the DAPCI ion source was coupled with a portable mass spectrometer and demonstrated to be a suitable analytical method that can be used for "near-instant", *in-situ* detection of polar alkylated benzenes and non-polar PAHs that are difficult to analyze [44]. The combination of the DAPCI was demonstrated for the direct detection of 1,2,3,5-tetramethylbenzene, pentamethylbenzene, hexamethylbenzene, fluoranthene, anthrancene, benzo[*k*]fluoranthene, dibenz[*a*,*h*]anthracene, acenaphthene, indeno[1,2,3-c,d]pyrene, 9-ethylfluorene, and 1-benzyl-3-methyl-naphthalene. The model compounds used in this study were chosen because these alkylated benzenes and PAHs are known to possess carcinogenic and mutagenic properties [45]. The results obtained indicate that these hydrocarbons can be detected from ambient surfaces instantly. The structural characterization of these PAHs was determined and confirmed using tandem mass spectrometry (MS/MS) [46-49].

3.0 Experimental

In a typical DAPCI MS experiment, a corona discharge is generated by applying a high DC voltage to a sharp needle and the reagent ions produced are directed pneumatically towards a surface using a carrier gas (e.g. nitrogen, helium). The analyte(s) is desorbed and ionised directly from the surface, presumably by a two-step mechanism involving thermal desorption followed by gas-phase ionisation [50]. The DAPCI ion source was placed 1-5 mm in front of a mass spectrometer,

while its electric potential was set to +3 kV and nitrogen was used as the carrier gas at a flow rate of 1 L/min. Approximately ~ 3 ng μL^{-1} of each sample in methanol solvent (100ppm) was deposited on a filter paper surface and analysed instantly without any sample preparation under a harsh environment.

3.1 PAHs analysis using DAPCI-MS

The DAPCI system used in this work has been described previously [51]. It consists of a stainless steel needle with an elongated tapered tip, connected to a high voltage power supply (Figure 3.1). The elongated tip projects from a Teflon capillary tube carrying a high velocity flow of gas. The carrier gas is directed towards a substrate/surface to desorb and ionise analyte(s) which may be present. The carrier gas used was nitrogen. The voltage applied to the electrode was typically +3 kV so as to produce a corona discharge in close proximity to the tip of the electrode. The source is optimally coupled to the atmospheric pressure inlet of the mass spectrometer placed at a distance of 2.5 mm [38].

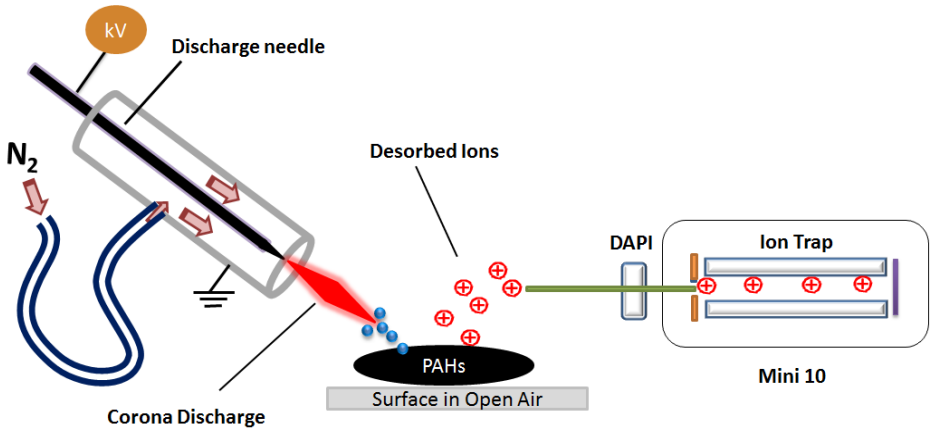


Figure 3.1 : Desorption atmospheric pressure chemical ionisation for direct analysis of PAHs using a miniature mass spectrometer (Mini 10).

3.1.2 *In-situ* Desorption Mass Spectrometry using a Miniature Mass Spectrometry

A DAPCI ion source was interfaced to a miniature mass spectrometer (Mini 10), built and characterized at Purdue University (Figure 3.1). The mass analysis system, the vacuum system, the control system and the detector are all integrated into a shoe-box sized aluminum box. The overall instrument uses 65 W average power and weighs <10 kg. The mass iiianalyzer is a rectilinear ion trap (RIT) [52] operating at a frequency of 1 MHz enclosed in a stainless steel manifold of 470 cm^3 volume [53]. As a result of its simplified geometry and pressure tolerance, RITs have several advantages for miniaturization evidenced in previous applications [54]. The operating pressure was in the range of 1 $x10^{-5}$ Torr to ca. 5 x 10^{-2} Torr, with mass analysis scans being performed in the lower pressure region [55, 56].

3.1.3 Interface to the Mini 10 Mass Spectrometer

To achieve an adequate vacuum, a discontinuous atmospheric pressure interface (DAPI) [57, 58] was used to directly introduce ions and the accompanying ambient air into the mass analyser from the ambient environment. The pressure rises on sample introduction but falls again to levels suitable for mass analysis when the interface is closed. DAPI has been used widely with miniature mass spectrometers [59, 60]. Unlike the conventional continuous ion introduction technique, DAPI admits discrete pulses of ion/air mixture to reduce the gas load on the pumps. In each sampling period the DAPI is opened for 10-20 ms under the control of a pulse valve. During this period, ions are pulsed into the vacuum system for subsequent analysis. After the DAPI is closed; the neutral gas is pumped away so that the trapped ions can undergo mass analysis.

3.1.4 Chemicals and Reagents

All the model standard compounds 1,2,3,5-tetramethylbenzene, pentamethylbenzene, hexamethylbenzene, fluoranthene, anthrancene, benzo[*k*]fluoranthene, dibenz[*a*,*h*]anthracene, acenaphthene, indeno[1,2,3-c,d]pyrene, 9-ethylfluorene, 1-benzyl-3-methyl-naphthalene were purchased from Sigma-Aldrich (St. Louis, MO) and used directly without further purification. SAFETY NOTE: Most of these compounds are known carcinogens. HPLC grade solvent (methanol) was purchased from Mallinckrodt Baker Inc. (Phillipsburg, NJ). Solutions were made up in methanol to the target concentration using stepwise dilution. In all the experiments sample preparation step was reduced to dilution of the model compounds in methanol solvent only.

3.4.0 Mass Spectrometry Instrumentation

In these experiments a commercial bench-top linear ion trap mass spectrometer (Thermo LTQ, San Jose, CA USA) was used for the initial experiments. The instrument was set to record mass spectra in the automatic gain control mode for a maximum ion trap injection time of 100 ms; three microscans were combined per spectrum as shown in Appendix B.1. MS/MS for structural elucidation was performed on the isolated molecular ions of interest using collision-induced dissociation (CID) to confirm the presence and identity of the analyte(s) [48]. These experiments were performed using an isolation window of 1.5 Thomson (Th. mass/charge units) and normalized collision energy of 25-40% (manufacturers unit). Mass and collisional energy calibration were carried out following the manufacturer's instructions.

3.4.1 *In-situ* analysis using a portable mass spectrometer

The DAPCI ion source was held 2.5 mm away from the inlet of the Mini 10 mass spectrometer as shown in Figure 3.1, to achieve rapid direct analysis of untreated samples under ambient conditions. Results from the *in-situ* analysis experiment were compared with those from a commercial bench-top instrument operating in a typical lab setting.

3.5.0 Results and Discussion

Analysis of the plasma generated from the DAPCI probe operated in ambient air, under the open laboratory environment, showed the presence of water cluster ions. In other words, the primary probing ions from a DAPCI source are protonated water clusters, which are able to facilitate analyte(s) ionisation via proton transfer [61]. However, the DAPCI parameters which includes; carrier flow rate, applied electric potential and distance from the DAPCI tip to the MS inlet, all influence the type of ions that are observed in DAPCI MS [38, 42]. For this reason, DAPCI ionisation was first optimized to ionise only the PAHs via proton transfer reaction on a commercial bench-top LTQ instrument; an optimized flow rate of 1 L/min, and a DAPCI potential of +3 kV was used in all experiments unless otherwise stated. For instance, at a high carrier gas flow rate (>3 L/min) both molecular radical cations ($M^{+\bullet}$) and protonated molecular species ($[M+H]^+$) were observed in the DAPCI-MS experiment (Figure 3.2). When 3 ng/µL of fluoranthene (MW 202) was applied on the paper surface and analysed using DAPCI-MS, two intense peaks at *m/z* 202 and

203 (molecular radical cations $M^{+\bullet}$ and protonated molecules $[M+H]^+$) were observed. At 1 L/min flow rate, however, only the protonated molecular species $[M+H]^+$ of fluoranthene (MW 202) at *m/z* 203 was observed (Figure 3. 2 (a) and (b)). The identity of the protonated molecule was confirmed using tandem mass spectrometry as shown in insert (ii) of Figure 3. 2. In subsequent experiments, other PAHs were also analysed under ionisation conditions that predominantly favoured proton transfer reactions as the ionisation mechanism of DAPCI; the a carrier gas flow rate of 1 L/min was used while maintaining other parameters such DAPCI potential at +3 kV, and distance between DAPCI and mass spectrometer inlet at 2.5 mm.

For the analysis of other PAHs, ~3 ng μL^{-1} (1 µL of 100 ppm solution) of each sample solution prepared in methanol was deposited onto a cellulose chromatography paper surface (Whatman, Maidstone, Grade 1 UK) and the data recorded using a commercial instrument (Appendix B.1 for details). The resulting mass spectra showed intact protonated molecules $[M+H]^+$ with little or no fragmentation, and no interfering side reactions. The absence of signal due to background ions from the DAPCI source is consistent with the high ionisation efficiency of most PAHs using plasma based ion sources, and reflects their relatively high proton affinities (PA), a well-known feature of many PAHs analysed using chemical ionisation [42]. The mass spectra recorded for dibenz[*a*,*h*]anthracene (MW 278), anthracene (MW 178) showed mainly the protonated molecule $[M+H]^+$ (Figure 3.3 (a)-(b) and protonating DAPCI conditions.

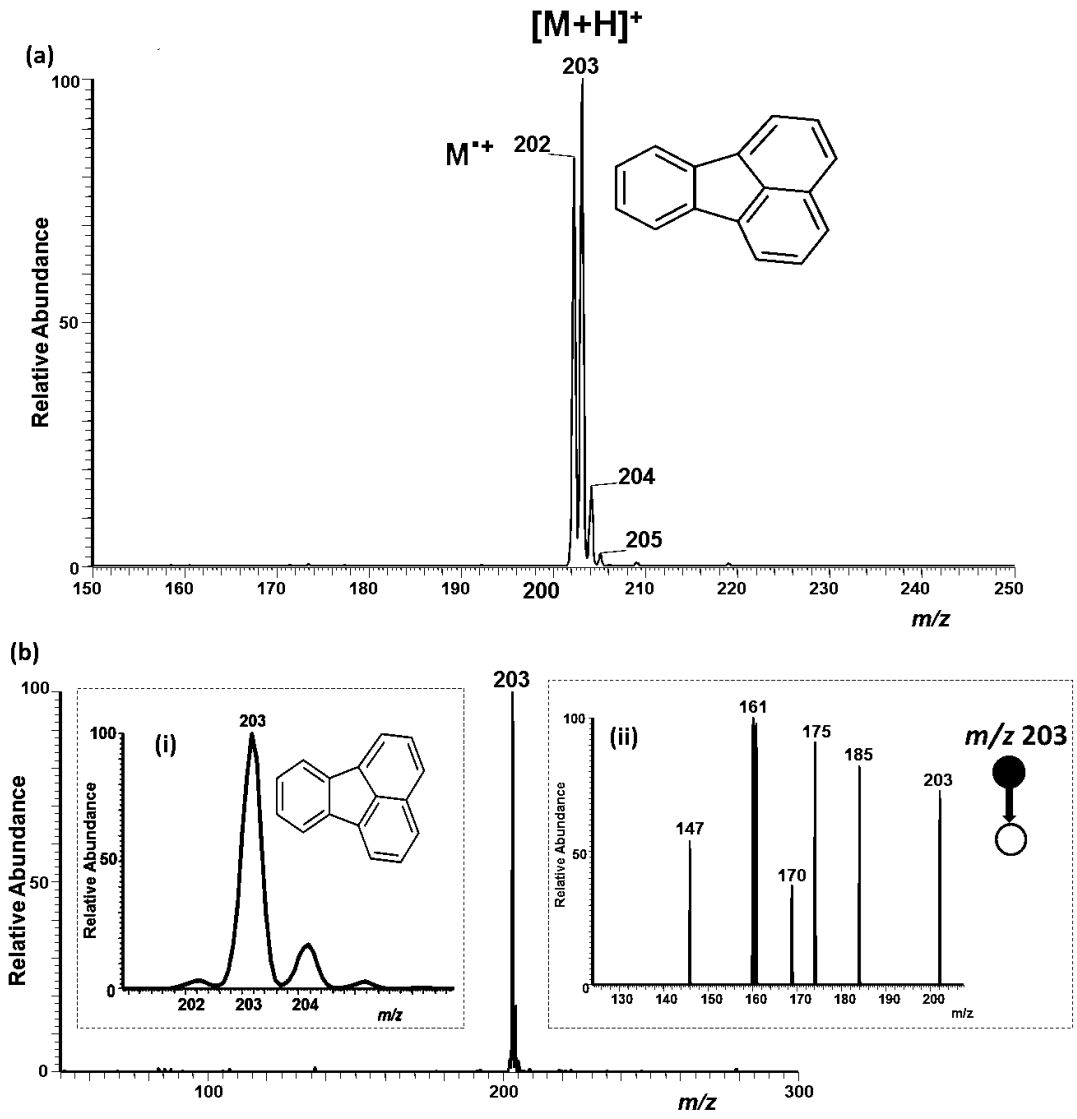


Figure 3.2 **:** Typical positive ion mode DAPCI mass spectra obtained using a bench-top ion trap instrument.3 ng μL^{-1} of the analyte(s) in methanol solution was spotted onto the surface and ionised in the open environment by application of an electric potential; (a) protonated fluoranthene $[M+H]^+$ (*m/z* 203), molecular radical cations at *m/z* 202 at 3.5 L/min carrier gas flow rate (b) only protonated molecular species $[M+H]^+$ of fluoranthene $[M+H]^+$ (*m/z* 203) at 1 L/min carrier gas flow rate was observed. Insert (i) shows the isotopic distribution of the analyte ion and insert (ii) shows MS/MS CID data for the selected ions again using 3 ng μL^{-1} of analyte in methanol solution.

Identification of each individual intact protonated molecule was achieved using MS/MS through CID experiments. For instance, the dissociation of dibenz[*a*,*h*]anthracene molecular ion of *m/z* 279 provided a fragment ion at *m/z* 264 via the loss of methyl [-15 Da or CH_3], Figure 3.3 insert (iv). Although this

fragmentation pathway is not common for many protonated organic compounds, the CID fragmentation pattern of dibenz[*a*,*h*]anthracene *m/z* 279 and anthracene (MW 178) ions observed in this experiment resembles the common fragmentation mechanisms seen for most ionic PAHs [62]: i) formation of $[M\text{-}H_n]^+$ fragment ions, and ii) ring opening and extensive isomerization leading to CH_3 and $(CH_2)_n$ (n > 1) losses [62]. Interestingly, unlike high energy collision processes, the low mass fragment ionic series $(C_nH_2)^+$ and $(C_nH_3)^+$ are not observed in our CID experiments.

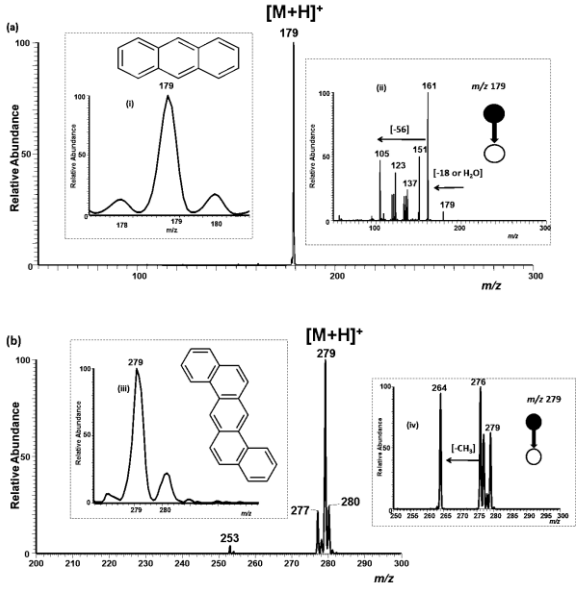


Figure 3.3 **:** Typical positive ion mode DAPCI mass spectra obtained using a bench-top ion trap instrument. 3 ng μL^{-1} of the analyte(s) in methanol solution was spotted onto the surface and ionised in the open environment by application of an electric potential; (a) protonated anthracene $[M+H]^+$ (*m/z* 179), (b) protonated dibenz[*a*,*h*]anthracene $[M+H]^+$ (*m/z* 279). Inserts (i) and (iii) shows the isotopic distribution of the analyte ion and insert (ii) and (iv) show MS/MS CID data for the selected ions using 3 ng μL^{-1} of each analyte in methanol solution for anthracene and dibenz[*a*,*h*]anthracene respectively.

Similarly, other alkylated benzenes and PAHs including 1,2,3,5-tetramethylbenzene, pentamethylbenzene, hexamethylbenzene, benzo[*k*]fluoranthene, acenaphthene, indeno(1,2,3-c,d)pyrene and 9-ethylfluorene

were analyzed using DAPCI-MS from the paper surface using the Thermo LTQ bench-top commercial instrument (Appendix B.2 and B.3 for their mass spectra and CID data). For example, Figure 3.4 shows the positive ion mode DAPCI mass spectrum obtained for the protonated molecule of alkyl substituted benzenes: (a) pentamethyl benzene (MW 148), and (b) hexamethyl benzene (MW 162). Again, characterization of each individual intact protonated molecule was achieved using MS/MS CID. For instance, Insert (ii)-(iv) Figure 3.4 shows that CID of the intact protonated $[M+H]^+$ of pentamethyl benzene at *m/z* 149 yields a single fragment ion of tetramethyl benzene molecule, which is deprotonated, at *m/z* 133, via a loss of methyl [-15 or $-CH_3$] (insert (ii) followed by the cocominat loss of [-26 Da] or C_2H_2 neutral loss. Also the protonated hexamethyl benzene molecule $[M+H]^+$ at *m/z* 163, followed the same CID dissociation fragmentation pattern with the loss of a methyl group [-15 or $-CH_3$] to give a deprotonated pentamethyl benzene fragment ion at *m/z* 147. Such fragmentation patterns from the multi-stage tandem mass spectrometry experiment allow definitive confirmation of the identity of the analyte [46, 63]. Table 3.1 provides a summary of data for all the model compounds studied, including their structures and CID fragmentation pattern.

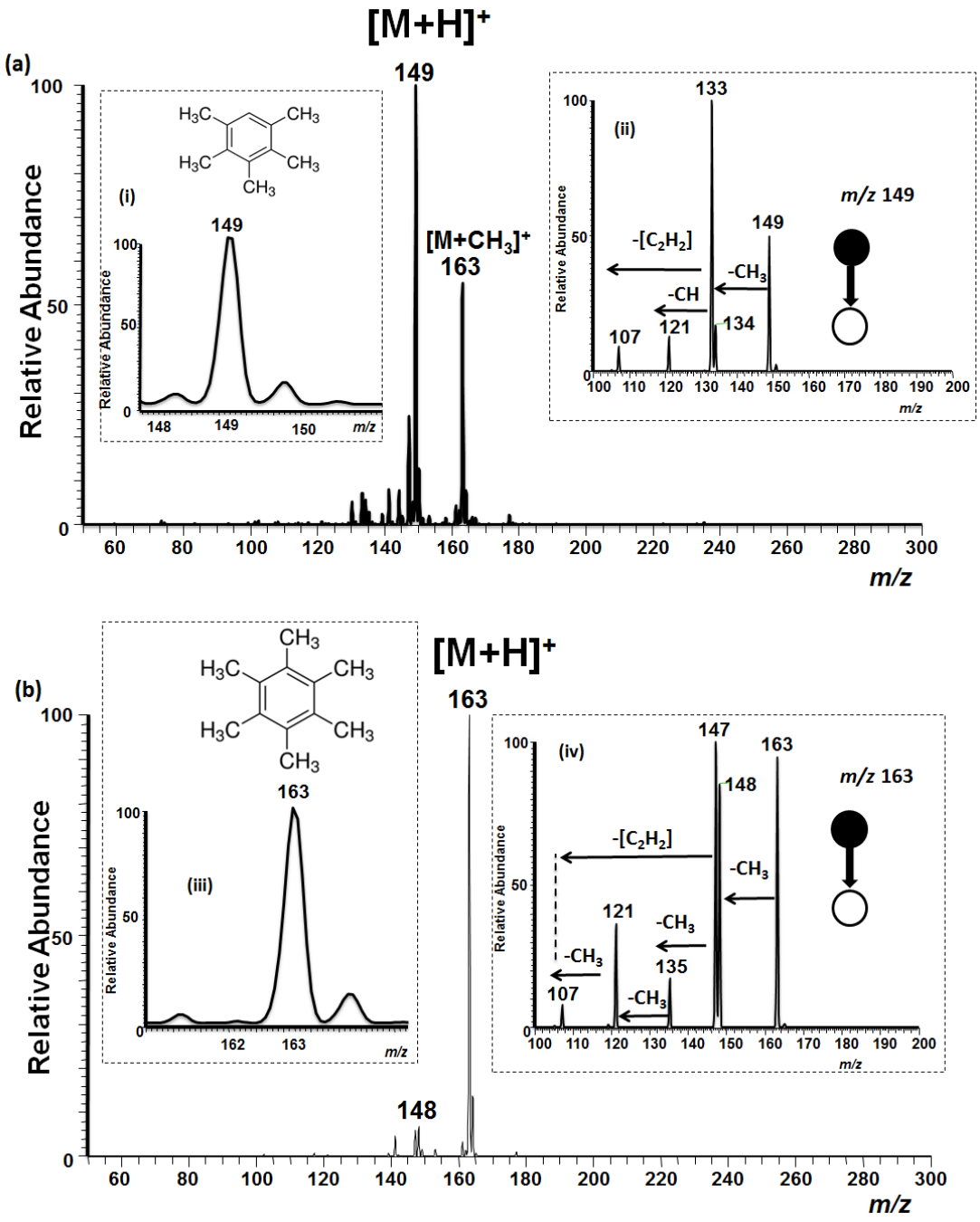


Figure 3.4 **:** Typical positive ion mode DAPCI mass spectra obtained using a bench-top ion trap instrument.3 ng μL^{-1} of the analyte(s) in methanol solution was spotted onto the surface and ionised in the open environment by application of an electric potential; (a) protonated pentamethylbenzene $[M+H]^+$ (*m/z* 149), (b) protonated hexamethylbenzene $[M+H]^+$ (*m/z* 163). Inserts (i) and (iii) shows the isotopic distribution of the analyte ion and insert (ii) and (iv) show MS/MS CID data for the selected ions again using 3 ng μL^{-1} of each analyte in methanol solution.

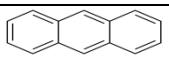
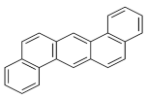
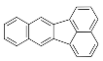
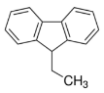
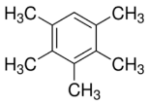
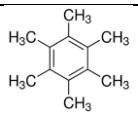
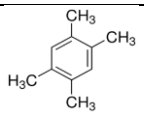
Compound Name	Chemical Structure	Molecular Weight	Ion Species Detected
Anthrancene		178	$[M+H]^+$
Dibenz[*a*,*h*]anthracene		278	$[M+H]^+$
Fluoranthene		203	$[M+H]^+$
Benzo[*k*]fluoranthene		253	$[M+H]^+$
Acenaphthene		155	$[M+H]^+$
Indeno[1,2,3-c,d]pyrene		276	$[M+H]^+$
1-benzyl-3-methyl-naphthalene		232	$[M+H]^+$, $M^{+\cdot}$
9- Ethylfluorene		194	$[M+H]^+$ $[M-H]^+$
Pentamethylbenzene		148	$[M+H]^+$ $[M-H]^+$ $[M-CH_3]^+$
Hexamethylbenzene		162	$[M+H]^+$
1,2,3,5-tetramethyl benzene		134	$[M+H]^+$

Table 3.1: Summary of Alkylated Benzenes and Polycyclic Aromatic Hydrocarbons (PAHs)

3.5.1 Analysis of PAHs in a mixture using DAPCI-MS

DAPCI-MS was also applied to the analysis of alkylated benzenes and PAHs in a mixture. For these experiments, an artificial mixture was prepared by mixing equal volumes of the model compounds: pentamethylbenzene, hexamethylbenzene, anthracene, dibenz[*a*,*h*]anthracen, fluoranthene, and benzo[*k*]fluoranthene) (1:1, v/v). The mixture was then analysed using the optimal DAPCI ionisation conditions that favor protonation under ambient conditions while restricting sample preparation to just dissolving the model compounds in methanol solvent. Approximately 3 ng μL^{-1} of each compound (mixed in methanol solution) were spotted onto the paper substrate and analysed using the commercial ion trap bench-top mass spectrometer. Figure 3.5 shows the mass spectra obtained from the analysis of the PAH mixture using DAPCI MS. Again, as noted for the individual PAH analysis, intact protonated molecules were observed $[M+H]^+$ and each individual molecule was characterized using MS/MS CID dissociation to identify each component in the mixture. The ability to restrict ion formation by proton transfer processes simplifies the resulting mass spectra in the case of mixture analysis without prior separation. The inserts (i) and (ii) in Figure 3.5 show the CID data for the protonated benzo[*k*]fluoranthene and dibenz[*a*,*h*]anthracene ions respectively. The PAHs mixture gave excellent stable DAPCI mass spectra and produced no observable ion fragmentations in the full scan mass spectrum mode.

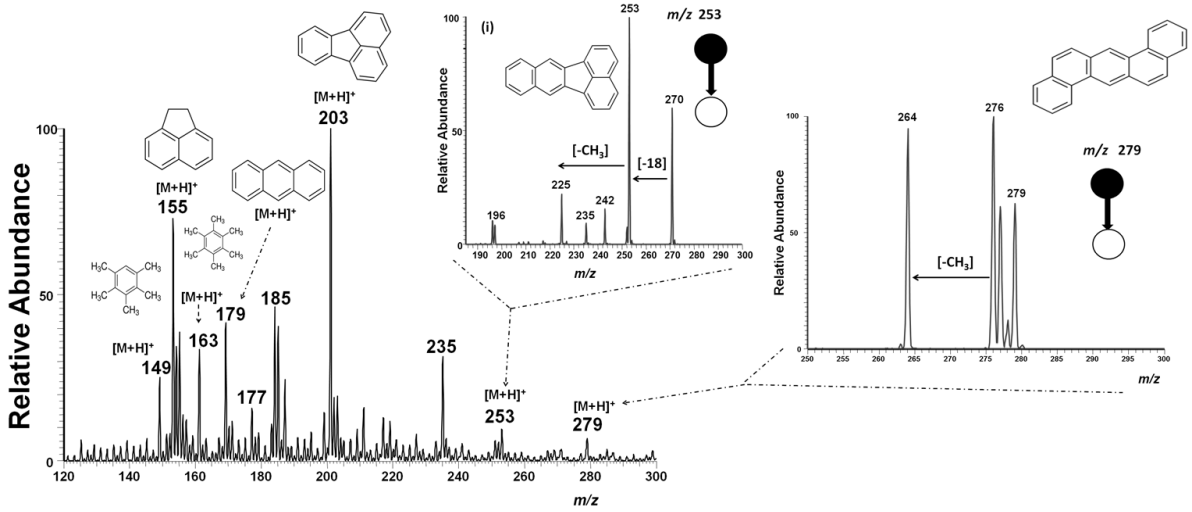


Figure 3.5: Positive ion mode DAPCI mass spectrum for a mixture of several of the model compounds analyzed using a bench-top instrument. All the compounds in the mixture gave intact protonated molecular species $[M+H]^+$ of; pentamethylbenzene (*m/z* 149), acenaphthene (*m/z* 155), pentamenthylbenzene (*m/z* 163), anthrancene (*m/z* 179), fluoranthene (*m/z* 203), benzo[*k*]fluoranthene (*m/z* 253), and dibenz[*a,h*]anthracene (*m/z* 279). Absolute amounts of analyte(s) spotted onto the surface and ionised in open environment by application of an electric potential were 5 ng μL^{-1} in methanol solution; inserts (i) – (ii) show MS/MS CID data for benzo[*k*]fluoranthene (*m/z* 253), and for dibenz[*a,h*]anthracene (*m/z* 279) protonated molecules using 3 ng μL^{-1} of each analyte in methanol solution.

3.5.2 Direct *in-situ* analysis of Alkylated Benzenes and PAHs using a Portable Mass Spectrometer (Mini 10) with DAPCI

The successful analysis of alkylated benzenes and PAHs using a commercial bench-top mass spectrometer with DAPCI encouraged us to transfer this experiment to a miniature ion trap mass spectrometer (Mini 10). Mixtures as well as individual PAHs were analysed in the same manner as above, with the aid of a commercial bench-top instrument using as well as with a miniature mass spectrometer Mini 10 coupled to a DAPCI ion source. For example, Figures 3.6 (a)–(c) show mass spectra

for 3 ng μL^{-1} 9-ethylflourene $[M+H]^+$, at *m/z* 195, acenaphthene $[M+H]^+$, at *m/z* 155, and hexamethylbenzene $[M+H]^+$, at *m/z* 163 respectively. Other model PAHs analysed using DAPCI with a portable mass spectrometer included: 1,2,3,5-tetramethylbenzene pentamethylbenzene and benzyl-3-methylnapthalene (see Appendix B.4 (Appendix B for more detail). As can be observed, coupling the DAPCI ion source to a portable mass spectrometer (Mini 10) gives a high signal-to-noise ratio even at this low level of analyte 3 ng μL^{-1} (Figure 3.6 d). Both the commercial and the custom built miniature instrument Mini 10 mass spectrometers give high ion signal-to-noise ratios that allow the identity of alkylated benzenes and PAHs to be readily confirmed by MS/MS. Even though the Mini 10 operates at a relatively higher pressure compared with the commercial instrument used, little fragmentation was observed in the full scan mass spectra as shown in Figure 3.6 (a)-(c).

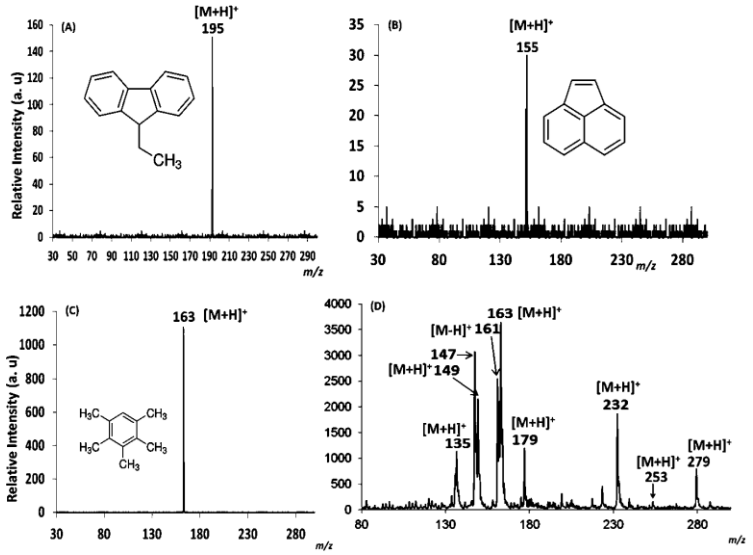


Figure 3.6 : Positive ion mode DAPCI mass spectra using a portable instrument. 3 ng µL-1 of the analyte(s) in methanol solution was spotted onto the surface and ionised in the open environment by application of an electric potential; (a) protonated 9-ethylfluorene [M+H]+ (m/z 195), (b) protonated acenaphthene $[M+H]^+$ *m/z* 155, (c) protonated hexamethylbenzene $[M+H]^+$ (*m/z* 163) and (d) seven PAHs model compounds in a mixture examined on a surface (paper substrate) analysed using a potable mass spectrometer. All the compounds in the mixture gave intact protonated molecular species $[M+H]^+$; pentamethylbenzene (*m/z* 149), hexamenthylbenzene (*m/z* 163), anthrancene (*m/z* 179), benyl-3-methylnapthalene (*m/z* 232), benzo[*k*]fluoranthene (*m/z* 253), and dibenz[*a*,*h*]anthrancene (*m/z* 279).

The combination of the DAPCI and Mini 10 was also used for PAH mixture analysis. A standard mixture (1:1 v/v) of pentamethylbenzene (MW 149), acenaphthalene (MW 154), hexamenthylbenzene (MW 163), anthrancene (MW 179), fluoranthene (MW 203), benzo[*k*]fluoranthene (MW 252), and dibenz[*a,h*]anthracene (MW 278), and benyl-3-methylnapthalene were dissolved in methanol solution. Figure 3.6 (d) shows all the components (3 ng μL^{-1} each) in the mixture were observed in the full scan mode with a portable mass spectrometer at expected *m/z* of $[M+H]^+$: pentamethylbenzene at *m/z* 149, acenaphthalene at *m/z* 155, pentamenthylbenzene at *m/z* 163, anthrancene at *m/z* 179, fluoranthene at *m/z* 203, benzo[*k*]fluoranthene at *m/z* 253, and dibenz[*a,h*]anthrancene at *m/z* 279. Here too, the alkylated benzenes and PAHs in the mixture were analysed from a paper surface.

3.5 Conclusions

The application of DAPCI ambient ionisation technique for the direct analysis of condensed phase alkylated benzenes and PAHs using a portable mass spectrometer has been studied. Analysis of different species was achieved through proton transfer reactions and was applied for selective ionisation of polar and non-polar hydrocarbons, individually and in a mixture in the open air under laboratory conditions. Fundamental aspects of the ionisation process were investigated in terms of ionisation mechanism and fragmentation patterns for different PAHs and alkylated benzenes. From the results shown, it is evident that different PAHs and alkylated benzenes can easily be ionised and detected with a DAPCI source coupled with a miniaturized portable mass spectrometer. The combination of DAPCI and a portable mass spectrometer has the potential to be an important analytical tool for *in-situ*

analysis of alkylated benzenes and PAHs on surfaces. Future work will involve on-site analysis and quantification of these compounds in real environmental samples. The capabilities of this analytical protocol will be extended to other environmental contaminants (e.g., crude oil) that are also of significant importance. The results shown are of interest beyond the alkylated benzenes and PAHs studied here as they demonstrate the feasibility of *in-situ* analyses using a portable miniaturized mass spectrometer for non-polar, condensed phase organic chemicals. This method could also be applied in other monitoring applications such as environmental hygiene, analysis in forensics studies and homeland security. The development of the solvent-free handheld DAPCI ion source version and it's application the trace detection of nitroaromatic explosives is presented in chapter 4 that follows.

3.6 References

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Chapter 4 : Handheld Portable DAPCI Ion Source for On-Site Point and Shoot Applications

4.0 Overview

A handheld, cylinder and solvent free, ion source weighing only 0.6 kg has been developed. It is based on desorption atmospheric pressure chemical ionisation (DAPCI) and has been used in the analysis of nitroaromatic explosives on surfaces in open air. Portability for in-field analysis is offered. A small, inexpensive rechargeable lithium polymer battery was used to power the custom-designed circuitry within the device, which generates up to ±5 kV DC voltage to ignite corona discharge plasma in air for up to 12 hours of continuous operation. The generated plasma is pneumatically transported to the surface to be interrogated by ambient air at a rate of 1-3.5 L/min, compressed using a small diaphragm pump. The plasma is directed onto a surface to interrogate analyte(s); liquid or solid samples may be rapidly examined without any sample preparation in the open environment. The advantages of low carrier gas and low power consumption (< 6 W), as well as zero solvent usage have aided the development of the field-ready, handheld device for trigger-based, "near real-time" sampling/ionisation.

Individual nitroaromatic explosives (such as 2, 4, 6-trinitrotoluene (TNT)) can easily be detected in amounts as low as 5.8 pg with a linear dynamic range of at least 10 to 100 pg, a relative standard deviation (RSD) of ca. 7% and an R^2 value of 0.9986. Direct detection of several nitroaromatic compounds in a complex mixture without prior sample preparation is also demonstrated and their identities were confirmed by tandem mass spectrometry fragmentation patterns.

4.1 Introduction

Increases in terrorism and security threats around the world necessitate the development of highly sensitive analytical techniques capable of detecting extremely low vapour pressure explosives *in-situ* at the source. These analytical tools should be capable of high throughput analysis in "near real time"; however, such methods are not currently available. Any method which can operate *in-situ* providing near instantaneous analysis would have significant implications for homeland security, border control, transportation security, national defence, and forensic investigations [1]. Condensed phase explosives are difficult to ionise due to their wide range of volatilities while their presence on surfaces makes it difficult for direct analysis and detection. *In-situ* analysis of condensed phase explosives and their residues with low vapour pressure with little or no sample preparation is therefore highly desirable [2, 3].

Currently the most widely adopted technology for the trace analysis and detection of explosives at border and transport checkpoints is wipe sampling coupled with ion mobility spectrometry (IMS) [4-7]. Although detection is instantaneous and low detection limits can be achieved, IMS is prone to poor selectivity and has difficulties associated with identification and confirmation of analyte(s) in complex mixtures due to interactions between the reagent gas and the matrix [8-10].

Solid phase extraction (SPE) [2, 11] followed by gas chromatography (GC) or liquid chromatography (LC) mass spectrometry (MS) [12, 13] is the most widely adopted method for both qualitative and quantitative analysis of explosives. High sensitivity and specificity can be achieved using SPE-GC/LC-MS for explosives analysis [14-17]. With the aid of tandem mass spectrometry (MS/MS) and ion molecule reactions, higher selectivity and specificity of trace amounts of explosives

in complex mixtures can be achieved [18-20]. Despite all these advantages a significant amount of time is required for sample pre-concentration and pre-treatment. Moreover, the sample must also be transported to the laboratory for analysis.

Recently ambient ionisation [21, 22] in conjunction with mass spectrometry has been used for the trace analysis and detection of a wide range of explosives measured *in-situ* at the site of interest [23, 24]. Ambient ionisation (AI) is a relatively new technique that facilitates both sampling and ionisation of analyte(s) in their native environment in one step outside the mass spectrometer with little or no sample preparation [25]. Ambient ionization mass spectrometry (AI-MS) analysis can be performed directly on unmodified samples in air outside the vacuum system and is capable of providing nearly instantaneous data while minimizing sample preparation [26-30].

AI-MS methods have shown extraordinary performance due to their simplified analytical procedures [21, 31-33]. For instance, in the past 10 years desorption electrospray ionisation (DESI),[34, 35] direct analysis in real time (DART) [36-38], plasma-assisted desorption/ionisation (PADI) [39], low temperature plasma (LTP) [40-42], desorption electro-flow focusing ionisation (DEFFI) [24] and desorption atmospheric pressure chemical ionisation (DAPCI) [38, 43-45] have been exploited in the trace detection and analysis of a wide range of explosives. However, these AI sources are usually limited to the laboratory settings due to the bulky gas cylinders, high electrical power, and high gases/solvent flow rates required for operation. These requirements make size reduction difficult and often lead to an increase in setup time. For example, the DESI ion source requires a syringe pump for ~3 μL/min solvent feed and high pressure gas flows [28, 31].

Desorption ionisation sources based on photo ionisation, such as desorption atmospheric pressure photoionisation (DAPPI) [46] have the ability to perform rapid analysis of a wide range of analyte(s) including explosives from surfaces [47]; however, they are not amenable for in-field analysis due to lack of portability. As such there exists a need for small, handheld, portable ambient ionisation sources that can be integrated with small footprint, portable mass spectrometers [48-50] for in field applications to interrogate different surfaces for the presence of different analyte(s) (e.g. explosives).

Plasma based AI sources are good candidates for portability due to their inherent lack of solvent and generated waste as well as the ability to change the discharge gas composition for improved desorption and ionisation capability [51]. For example, low temperature plasma (LTP), a plasma-based AI source based on dielectric barrier glow discharge, has been successfully miniaturized and its performance demonstrated on both a commercial bench-top and on a miniature mass spectrometer [52]. DAPCI is another plasma-based AI source that is relatively underutilized. DAPCI is based on atmospheric pressure chemical ionisation (APCI) [53]. DAPCI has been successfully utilized in the analysis of complex molecules including melamine in powdered milk [54], for the differentiation of variants of Chinese tea [55], analysis of fuels and petroleum oil mixtures [56], and analysis of alkylated benzenes and polycyclic aromatic hydrocarbons [57]. In a typical DAPCI mass spectrometry (DAPC-MS) experiment, a corona discharge is generated by applying a high DC voltage to a sharp needle and the gas phase reagent ions produced are directed pneumatically towards a surface using a carrier gas (e.g. nitrogen, helium, argon). The analyte(s) is desorbed and ionised directly from the surface, presumably by a two-step mechanism involving thermal desorption followed

by gas-phase ionisation, through proton or electron transfer, electron capture or other ion molecule reactions under ambient conditions in open air [35].

In this chapter the development of the first portable handheld DAPCI ion source and its application to the direct analysis of nitroaromatic explosives from surfaces in the open environment is presented. The entire developed handheld DAPCI ion source, including the air pump, battery and electronic circuitry is enclosed in a 3D printed plastic enclosure. The developed handheld DAPCI is applied for "near real time" *in-situ* detection and analysis of nitrobenzene explosives under ambient conditions without sample treatment and their chemical identity is confirmed using tandem mass spectrometry (MS/MS) [19, 58]. Results obtained from the handheld portable DAPCI-MS experiments using a bench-top mass spectrometer show that the handheld portable DAPCI ion source can be used to detect model nitroaromatic explosive compounds (in the low pg range for TNT) from a paper surface (surface area <~1 cm^2). The sample preparation is limited to the dilution of the explosive standards in methanol/acetonitrile solvent (v/v, 1:1) to simulate different levels of explosives encountered in real scenarios.

4. 2.0 Experimental

4.2.1 Chemicals and Reagents

All analytical explosive standards of 2, 4, 6-trinitrotoluene (TNT), 1, 3, 5-trinitrobenzene, 2, 4-dinitrotoluene, 1, 3-dinitrobenzene, 2-amino-4, 6-dinitrotoluene and 2, 4, 6-trinitrophenylmethylnitramine (Tetryl) were purchased as 1 µg/mL solutions in methanol/acetonitrile (1:1) from AccuStandards Inc. (New Haven, CT). A stock solution multicomponent mixture of explosives 2, 4, 6-trinitrotoluene

(TNT), 1, 3, 5-trinitrobenzene, 2, 4-dinitrotoluene, 1, 3-dinitrobenzene, 2-amino-4, 6-dinitrotoluene, 2, 4, 6-trinitrophenylmethylnitramine (Tetryl) (100 µg/mL each component) in methanol/acetonitrile (1:1) solution was also purchased from the same supplier. HPLC grade solvent (methanol and acetonitrile) was purchased from Mallinckrodt Baker Inc. (Phillipsburg, NJ). Working solutions of the samples (10-100 pg/µL) were made up in methanol and acetonitrile to the target concentration using stepwise dilution.

4.2.2 Sample Preparation

In all experiments the sample preparation step was reduced to dilution of explosive stock solutions in methanol/acetonitrile (1:1) to the desired concentration. From each sample solution approximately, 1 µL was applied onto a cellulose filter paper (Whatman, Maidstone, UK Grade 1) (1 cm^2 total surface area) using a pipette (Brand Gmbh, Germany). All samples were analysed immediately in open air using the newly developed handheld, portable DAPCI device coupled to a commercial mass spectrometer.

4.2.3 Handheld Portable DAPCI Ion Source

A custom designed handheld solvent-free, portable DAPCI ion source has been developed; it differs from the normal DAPCI ion source reported previously [53, 56]. It consists of a tapered tip stainless steel needle (80 mm long and 3.2 mm diameter tapered to a fine point) inserted coaxially into a Swagelok 1/8" Teflon tee piece with a custom designed ceramic exit nozzle attached to a grounded electrode. The stainless steel needle was connected via a barrel connector to the high voltage

output module. A small diaphragm pump (Schwarzer Precision, 12FC35A) with a maximum flow rate of 6 L/min was used to generate and compress an air flux inside the handheld DAPCI device (see Figure 4.1 b) for more details). The generated air is ionised by the corona discharge and pneumatically transported to the surface to desorb and ionise analyte(s) that may be present. The corona discharge is formed by applying a high voltage (typically ± 2.5 – 3kV, generated using a high voltage DC to DC converter, EMCO High Voltage, c50/c50N) to a tapered tip stainless steel needle powered using a lithium polymer battery (Tracer Power, 12 V 4, Ah).

Figure 4.1 a) shows the custom-designed high voltage control circuit used to generate the high voltage in the range of ±1 - 5 kV. Figure 4.1 c) shows a photo of the fully packaged handheld portable DAPCI ion source housed in a 3D printed plastic enclosure (Maker Bot Replicator 2, Robo Savvy, UK). The circuitry of the handheld, portable DAPCI is powered from a 12 V, 4 Ah lithium Polymer battery with a built-in charging circuit and a power level indicator that displays when re-charging is necessary. From a fully charged state the battery can power the device for up to 12 hours of continuous use and for as much as 3-4 days when used intermittently. It should be noted that the total operation time of the handheld portable DAPCI ion source in the field is much longer, considering that the power supply is only triggered as needed and that the diaphragm pump may also be turned off while not in use, leading to prolonged lifetime. The high voltage regulated DC-to-DC converter module (EMCO HIGH VOLTAGE, c50/c50N, UK) and the diaphragm pump (Schwarzer Precision, 12FC35A, UK) require a minimum 12V supply to operate correctly. Due to the battery discharge rate, it was necessary to include a buck-boost DC-to-DC converter to ensure precise voltage regulation. An ARM based microcontroller board (Teensy 3.1, PJRC, USA) handles all internal

command communication and receives user inputs via a 2.4” touch screen interface (4D-Systems, 24PT-uLCD, UK). This enables the user to switch between ion polarities (positive or negative) and to regulate voltage in either positive or negative mode. The exact voltage applied to the needle and the flow rate of the compressed air exiting the diaphragm pump can also be regulated via the touch screen. The high voltage DC-to-DC converter module is programmed via a precision voltage reference and digital potentiometer that has its wiper position set via commands from the micro-controller. The pump speed is controlled by digitally altering the duty cycle of the Pulse Width Modulated (PWM) signal that turns on the MOSFET driver for the diaphragm pump (see Figure 4.1 a). Figure 4.1 c) shows a photograph of the entire handheld, portable DAPCI ion source housed in the 3D printed plastic enclosure (MakerBot Replicator 2, Robo Savvy, UK).

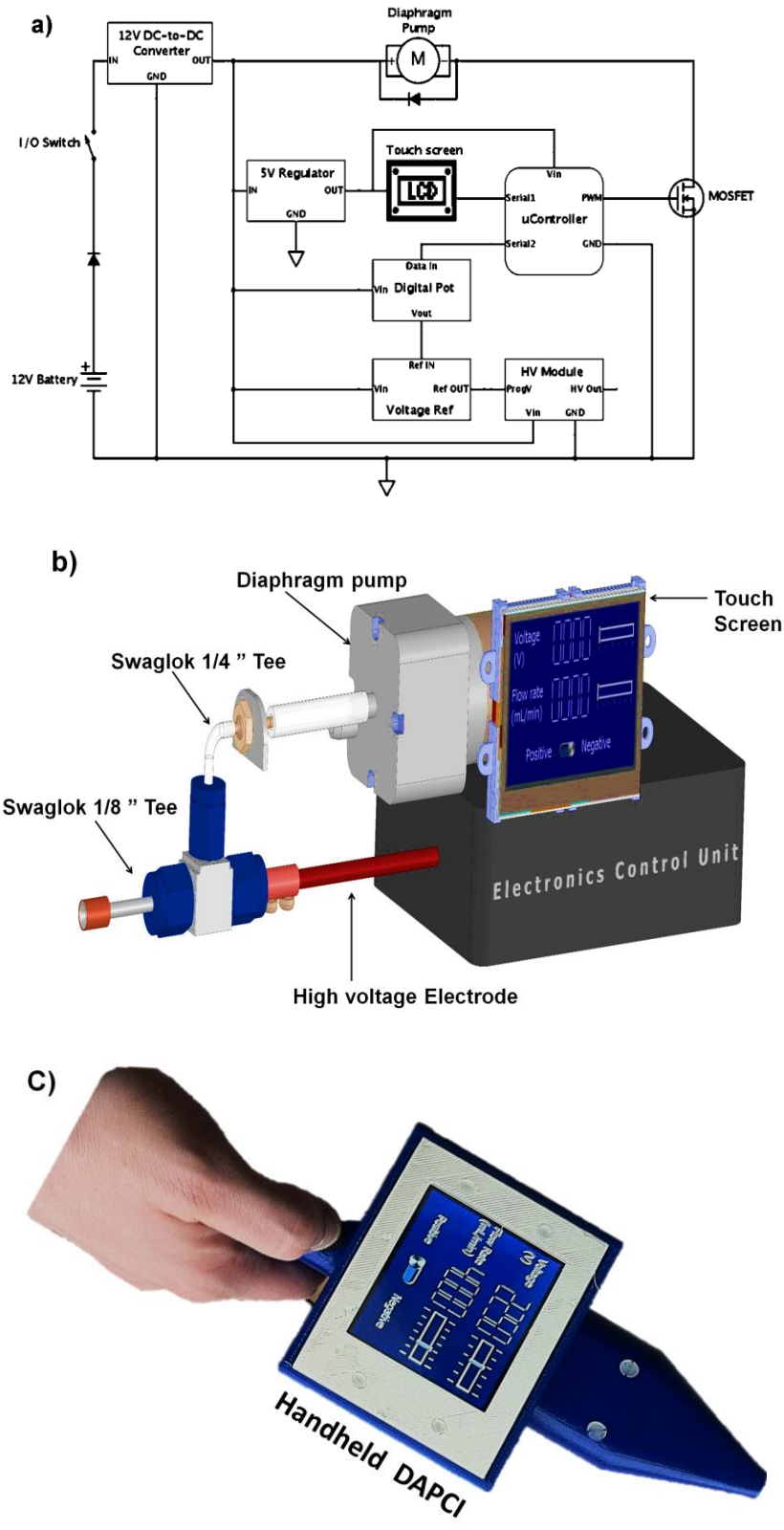


Figure 4.1**:** Handheld, portable desorption atmospheric pressure chemical ionisation (DAPCI) source for direct analysis of explosives: a) circuit block diagram, b) CAD model of internal DAPCI components, c) photograph of the handheld DAPCI ion source.

4.2.4 Handheld portable DAPCI Coupled to a Mass Spectrometer

In a typical DAPCI-MS experiment, a corona discharge is generated by applying a high DC voltage to a sharp needle and the reagent ions produced are directed pneumatically towards a surface using a carrier gas (e.g. air, nitrogen, helium) [35, 56]. The carrier gas is directed towards a substrate/surface at a rate of ~3 L/min to desorb and ionise analyte(s) which may be present. The voltage applied to the electrode was typically ±~2.5 - 3 kV so as to produce a corona discharge in close proximity at the tip of the electrode. The source is optimally coupled to the atmospheric pressure inlet of a commercial benchtop mass spectrometer placed at a distance of ~2.5 mm (Figure 4.2). The analyte(s) ions formed are transported to the mass spectrometer through the atmospheric pressure interface. The transport mechanisms for this action includes static charge accumulation on the insulating surface, momentum transfer in the case of gaseous ion/charge micro-droplet impact on the molecular species on the surface, and the suction of the vacuum at the inlet of the transfer capillary.

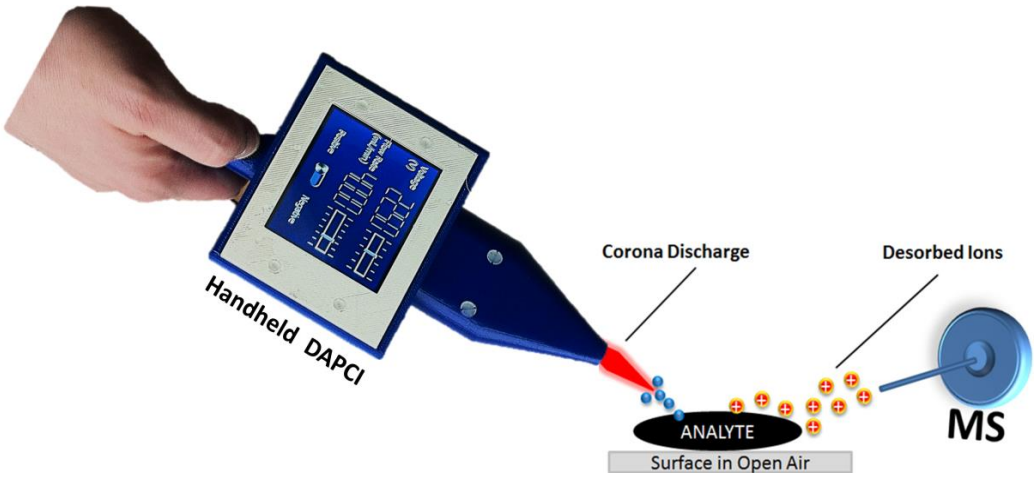


Figure 4.2 **:** Handheld DAPCI experimental setup used in the analysis of nitroaromatic explosives.

Experiments were conducted using a commercial linear ion trap (Thermo LTQ, San Jose, CA USA) mass spectrometer with an atmospheric pressure interface, tuned for optimum detection of the precursor ion of interest. Data processing was carried out using the commercial instrument software interface (Xcalibur, version 4.1). The experimental conditions for operation of the handheld portable DAPCI-MS for nitroaromatic explosives (2, 4, 6-trinitrotoluene (TNT), 1, 3, 5-trinitrobenzene, 2, 4-dinitrotoluene, 1, 3-dinitrobenzene,2-amino-4, 6-dinitrotoluene, 2, 4, 6-trinitrophenylmethylnitramine (Tetryl)) and the multi component explosive mixture for analysis in the positive mode were as follows: handheld, portable DAPCI ion source voltage applied to the tapered tip stainless steel needle of +3 kV; tube lens voltage, 200 V; heated capillary voltage, 25 V; capillary temperature, 200 ^{o}c; multipole rf amplitude (V_{p-p}), 400 V; multiplier voltages 1 and 2, -800 V; ion injection time, 100 ms and 3 microscans. For the analysis of the same standard model compounds and the multi-component explosive mixture in negative mode the conditions were as follows: handheld, portable DAPCI ion source voltage applied to the tapered tip stainless steel needle of -2.5kV; tube lens voltage, -102 V; heated capillary voltage, -20 V; capillary temperature, 200 ^{o}c; multipole rf amplitude (V_{p-p}), 400 V; multiplier voltages 1 and 2, -800 V; ion injection time, 100 ms and 5 microscans. For all experiments in both positive and negative ion modes the instrument was set to record mass spectra in the automatic gain control mode for a maximum ion trap injection time of 100 ms. All mass spectra were recorded as peak profiles with an averaging time of 1 min and are presented with the background subtracted unless otherwise stated. For structural confirmation MS/MS was performed on the isolated molecular ion signals of interest using collision-induced dissociation (CID) to confirm the presence and identity of the analyte(s) [13]. These

experiments were performed using an isolation window of 1.5 thomson (Th. mass/charge units) and using normalized collision energy of 25-40% (manufacturer's unit). Mass and collisional energy calibration were carried out following the manufacturer's instructions.

The mini-DAPCI ion source was placed ~2.5 mm in front of the mass spectrometer, while its electric potential was set accordingly and air generated using a diaphragm pump was used as the carrier gas at a flow rate of 3 L/min. Approximately ~1 µL of each sample in methanol: acetonitrile solvent was deposited on a cellulose paper (Whatman, Maidstone, UK Grade 1) surface and analysed in both positive and negative MS modes without any sample preparation under ambient conditions.

4.3.0 Results and Discussion

Figure 4.1 displays the handheld portable DAPCI block diagram, photograph and circuit schematic. The overall weight of the source is 0.6 kg which is reduced to 0.3 kg when the diaphragm pump is replaced with an external gas connection line. The parts of the source are easy to assemble and inexpensive, with most of the cost being that of the voltage DC-to-DC converter module. The incorporation of the diaphragm pump for air generation as a corona discharge gas reduces the size of the DAPCI; however, this increases the power requirement for the source from 4 W to 6 W, and the weight from 0.3 kg to 0.6 kg (Table 4.1: DAPCI specification)

Specification	Value
Ion Polarity	Positive or Negative
Voltage Range	0 to ±5 kV
Air Flow Rate (using an internal diaphragm pump)	0 to 6 L/min
Max Power Consumption	6 W
User Interface	Touch screen LCD and physical switch
Battery Charging Voltage	12 V DC
Lithium Battery Capacity	12 V 4 Ah
Total Weight	0.6 kg

Table 4.1: **Handheld DAPCI Specification**

4.3.1 Handheld Portable DAPCI-MS Characterization

The handheld, portable DAPCI ion source was first characterized by recording the background mass spectrum of the corona discharge using air as the discharge gas generated using a small diaphragm pump in the open laboratory environment in both positive and negative ion modes. The primary reagent ions from the handheld, portable DAPCI source are protonated water clusters $[(H_2O)_nH]^+$, and anions (O_2^-, OH^-, NO_2^-). These ions facilitate analyte(s) ionisation via proton transfer and electron capture reactions in positive and negative ion modes respectively [59].

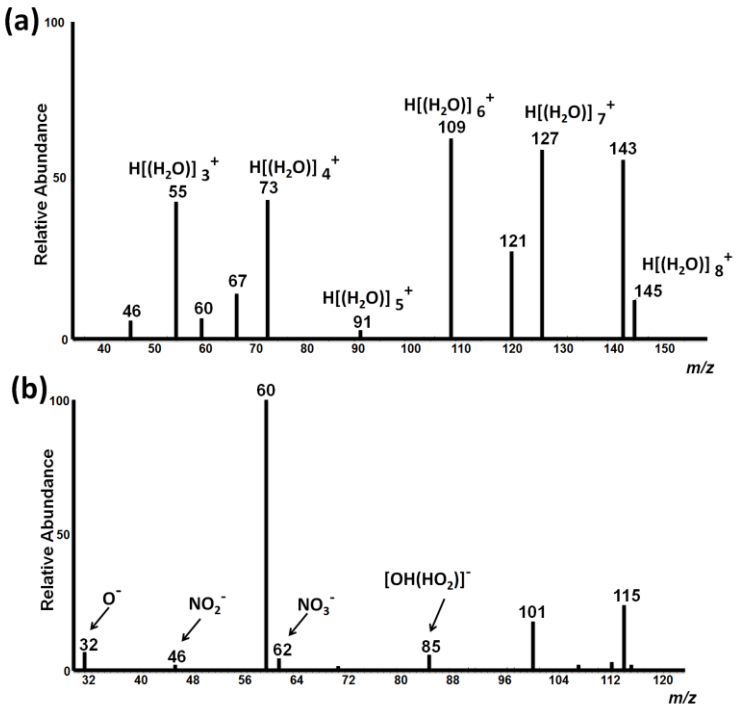


Figure 4.3**:** Typical mass spectra showing the portable DAPCI background ion signal of air discharge gas generated using a small diaphragm pump at a flow rate of 3 L/min obtained in: (a) positive mode at + 3 kV (b) negative mode at -2.5 kV and recorded using a bench-top ion trap instrument.

Figure 4.3 shows the typical background mass spectra obtained using the handheld portable DAPCI ion source. These spectra were recorded with the exit of the DAPCI ion source positioned approximately 2.5 mm away from the mass spectrometer inlet while the DAPCI needle voltage was set at 3 kV (in positive mode) via the touch screen. In the positive mode, protonated water clusters $[(H_2O)n + H]^+$ (n = 3, 4, 5, 6, 7 and 8) are observed at *m/z* 55, 73, 91, 109, 127, and 145[56]. Peaks at *m/z* 46, and *m/z* 60 presumably correspond to the NO_2^+ and CO_3^+ cations as observed previously [60]. The peaks in Figure 4.3 (a), at *m/z* 60 and 67 are not identified. The NO_2^+ and CO_3^+ peaks at *m/z* 46 and 60 are significant despite their relatively low abundance, because NO_2^+ and CO_3^+ are highly reactive ions which can undergo a variety of ion/molecule reactions including nucleophilic

addition, proton transfer, charge exchange, and oxidation. On the other hand a completely different background spectrum resulted (Figure 4.3 (b) when the handheld DAPCI ion source was operated in the negative mode at -2.5 kV set via the touch screen. The spectrum recorded in the negative mode showed deprotonated water cluster ion peaks of $[OH(H_2O)_3]^-$, and $[OH(H_2O)_4]^-$ at *m/z* 71 and 85 respectively [60, 61]. Intense peaks at *m/z* 32, 46, 60 and 62 correspond to anions of oxygen (O_2^-), nitrogen dioxide (NO_2^-), nitrogen trioxide (NO_3^-), and carbon trioxide (CO_3^-), respectively. Again these anions NO_2^-, O_2^-, CO_3^- are highly reactive species and can undergo a variety of ion/molecule reactions including nucleophilic addition, proton abstraction, charge exchange, and oxidation. These dominant water cluster protonated ions are known as the "first hydrated shell" and are formed by the core ions H_3O^+ and OH^- becoming hydrated with water vapour in ambient air.

4. 3. 2 Analysis of Nitrobenzene Explosives in Air using Handheld Portable DAPCI Ion Source in Negative Ion Mode

When air is used as the handheld DAPCI carrier gas under the conditions in Figure 4.3 (b); the ionisation of oxygen gas in the presence of water clusters generates reactant anions as observed in Figure 4.3 (b) at *m*/*z* 46, 32, and 60 (NO_2^-, O_2^-, CO_3^-) which readily react with condensed vapour phase nitroaromatic explosives [59, 62]. Such reactions are likely due to their high electron affinities (EA), a well-known feature of the nitro or nitrate functional groups present in most common explosive formulations [63-65]. This means that these analyte(s) can readily form negative ions by electron capture.[66, 67] This property of explosives has been previously exploited by other ambient ionisation methods such as DESI,[24, 68, 69] LTP [70, 71], and DART [72]. Just as DESI, DART and LTP have been used in the negative ion mode to detect TNT at trace levels, so also the handheld DAPCI ion

source was used in the negative ion mode to detect and record a mass spectra of TNT in full MS mode, when 10 pg (absolute concentration) of TNT in methanol/acetonitrile was deposited onto a filter paper surface area of approximately 1 cm^2 (Figure 4.2).

The mass spectra recorded in the negative ion mode for both TNT (Mw 227) and 1,3,5-trinitrobenzene (TNB) (Mw 213) was dominated by deprotonated molecular anions $[M-H]^-$ at *m/z* 212 and a moderately intense molecular anion species $[M]^-$ at *m/z* 213 formed by deprotonation and electron capture respectively, as displayed in Figure 4.4. The TNT fragments due to the neutral loss of NO *at m/z* 197 ($[TNT-NO]^-$), OH at *m/z* 210 ($[TNT-OH]^-$), deprotonated molecule at *m/z* 226 ($[TNT-H]^-$) and the abundant molecular anion at *m/z* 227 ($[TNT]^-$) due to electron capture were observed (Figure 4.4 a). Also a moderate reaction product at *m/z* 243 (oxidized adduct) is observed when 1 µL of TNT (Mw 227) was deposited on the paper surface. The peaks at 226, 227 and 243 correspond to the deprotonated ion $[M-H]^-$, the radical molecular anion $[TNT]^-$ and the oxidized adduct $[TNT+O]^-$ ions respectively. The peaks at *m/z* 210 $[TNT-OH]^-$ and 197 $[TNT-NO]^-$ correspond to the fragments formed by a neutral loss of the HO radical and the NO group, respectively, as confirmed by MS/MS (insert (i) Figure 4.4). It is important to note that the mass spectrum of TNT was identical to that previously observed in the negative ion mode using DESI [73] and LTP [35]. Similarly, for TNB ; in addition to the less intense molecular anion at *m/z* 213 and a high intense deprotonated the ion species $[M-H]^-$ at *m/z* 212, fragments with moderate intensity at *m/z* 196 -[TNB-OH] and at *m/z* 183 -[213-NO] were observed and confirmed by CID MS/MS data (Insert (ii) Figure 4.4 b). Insert (i), Figure 4.4 displays the product ion scan MS/MS spectrum of the oxidized TNT ion $[TNT+O]^-$ at *m/z* 243 which upon collisional activation yields a

major fragment peak at 213 which presumably corresponds to loss of hydroxide elimination that yields a minor deprotonated TNT molecule $[TNT\text{-}H]^-$ at *m/z* 226. The product ion MS/MS spectra of the less intense TNB (Mw 213) molecular anion [M]- at *m/z* 213 is shown in the insert (ii) Figure 4.4 b. The main fragmentation pathways of TNB (Mw 213) $[M]^-$ are neutral losses of $^-$[17 or OH] at *m/z* 196, $^-$[30 or NO] at *m/z* 183 and -[46 or NO_2] at *m/z* 167 as shown in insert (ii) Figure 4.4.

Compound	*LOD using a handheld ambient ion source (pg)	
	DAPCI **Using Air**	**LTP** **Using Helium**
2,4,6-trinitrotoluene (TNT)	5.8[x]	20
2,4-dinitrotoluene	6.5[x]	n.d
Tetryl	1500[x]	2000

***LOD** was calculated as, $LOD = 3.3\frac{standard\ error}{slope}$ taken from a calibration curve of 5 points with three repetitions for each point.

n.d = not detected

X= Precision range ± 4.5 to 8.5%

Table 4.2: LOD of the analysed nitroaromatic explosive model compounds in pg (absolute concentration). Comparison between handheld DAPCI using air and handheld LTP using Helium.[52]

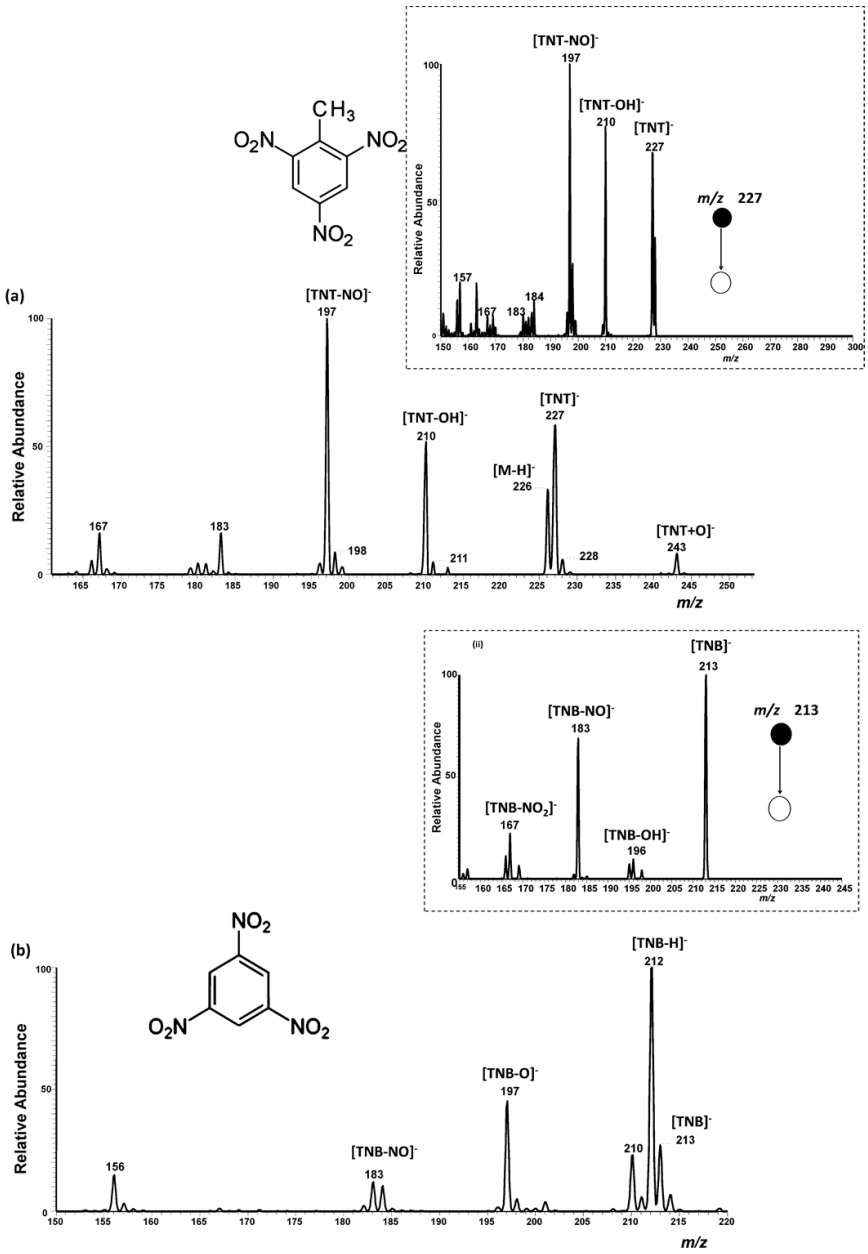


Figure 4.4: Typical handheld DAPCI ion source negative mass spectra obtained using a bench-top ion trap mass spectrometer instrument. 10 pg of TNT (Mw 227) and TNB (Mw 213) model explosive compounds in methanol solution were spotted onto a paper (~ 1 cm^2 surface area) surface and ionised in the open environment; (a) 2, 4, 6-trinitrotoluene (TNT) anion $[M]^-$ (*m/z* 227) and deprotonated ion at *m/z* 226 (b) TNB $[M]^-$ (*m/z* 213) and deprotonated ion $[M-H]^-$ at *m/z* 212. Inserts (i) and (ii) shows the CID MS/MS mass spectra of TNT (Mw 227) and TNB (Mw 213) radical anion $[M]^-$ at *m/z* 227 and 213 respectively.

As can be observed from Figure 4.4 above, the handheld DAPCI ion source gave a stable signal in the negative mode, with a high signal-to-noise (S/N) ratio

even at low concentrations of the explosive analyte(s) deposited on the paper surface. The abundance of radical anion $[TNT]^-$ at *m/z* 227 was used to prepare the five point calibration curve covering the range from 10 pg to 100 pg. A limit of detection (LOD) of 5.8 pg (absolute concentration) was obtained when analysed under ambient conditions in the open environment (Appendix C.1).

The analytical performance of the handheld DAPCI ion source for the analysis of nitroaromatic explosives was evaluated using full scan mass spectra of TNT in the negative mode over a range of absolute amounts from 10 to 100 pg and triplicate measurements showed good reproducibility with an RSD of 7% for a 10 pg/µL sample deposited on the paper surface (Appendix C.1). The handheld DAPCI ion source response was linear over the range 10 to 100 pg ($y = 2.786x+0.0$ with an R^2 value of 0.999). Using the Handheld DAPCI ion source the LOD for the model nitroaromatic explosive compounds studied was similar to that obtained using a handheld LTP ion source [52], as summarized in Table 4.1. Note that quantification based on MS/MS data is also possible but was not utilized.

In the subsequent experiments other explosive nitrobenzene compounds such as 2, 4-dinitrotoluene (Mw 182), 1, 3-dinitrobenzene (Mw 168), 2-amino-4, 6-dinitrotoluene (Mw 197) , 2, 4, 6-trinitrophenylmethylnitramine (Tetryl) (Mw 287) were analysed, in the negative mode, under conditions that favoured electron capture and proton abstraction as the ionisation mechanism as shown in Figure 4.3 (b). It is important to re-iterate that air was used as the carrier gas. A mass spectrum was recorded for each compound 2,4-dinitrotoluene (Mw 182), 1,3-dinitrobenzene (Mw 168), 2-amino-4,6-dinitrotoluene (MW 197), 2,4,6-trinitrophenylmethylnitramine (Tetryl) (Mw 287) by depositing approximately 1 µL of each sample solution prepared in methanol/acetonitrile (v/v 1:1;10 pg/µL) on a filter paper (~ 1 cm^2 surface

area) surface. The resulting mass spectra showed the intact radical anion $[M]^-$ and deprotonated or hydride subtracted molecules $[M-H]^-$ species with little or no fragmentation and no interfering side reactions (for more details see supporting information, Appendix C. 2). The absence of signal due to background ions from the handheld DAPCI source is consistent with the high ionisation efficiency of most explosives in the negative ion mode and reflects their relatively high electron affinity EA [64]. For instance radical anion $[M]^-$ was observed for 1, 3-dinitrotoluene (Mw 168) at *m*/*z* 168 ,while for 2,4-dinitrotoluene both molecular anion $[M]^-$ and hydride subtracted ion species $[M-H]^-$ were observed at *m*/*z* 182 and 181 respectively (Appendix C.2 b).

Identification of each individual intact radical anion and deprotonated molecule was again achieved using MS/MS through CID experiments. For example the dissociation of 1,3-dinitrotoluene (Mw 168) radical anion at *m/z* 168 provided an abundant fragment ion at *m/z* 138 via a neutral loss of NO as shown in insert (ii) (Appendix C. 2 b). Table 4.3 provides a summary of data for all the explosive compounds detected using the handheld DAPCI including their structures, vapour pressures and CID fragmentation patterns sampled at ambient conditions in the open environment using a cylinder-and-solvent-free handheld DAPCI ion source. When air is used as the handheld DAPCI ion source carrier gas to generate a corona discharge, ion species corresponding to OH and O- adducts were observed and their characteristic fragmentation of OH and NO losses (for more detail see Appendix C.2 d). Formation of these complexes/adducts and their characteristic fragmentation patterns provides reliable and complementary chemical information which facilitates nitrobenzene explosives identification in complex mixtures with enhanced sensitivity.

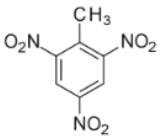
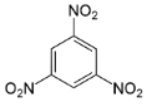
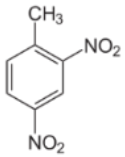
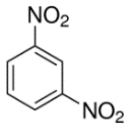
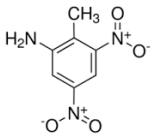
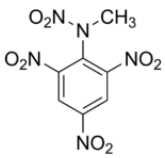
Compound Name	Chemical Structure	Vapor Pressure (Torr)	Mw	Ions Species Detected	MS^2 Transition
2, 4, 6-trinitrotoluene (TNT)		4.50×10^{-2} [74]	227	$[M]^-$, $[M-H]^-$	227 → 210 (Loss of 17 or OH) 227 → 197 (Loss of 30 or NO)
1, 3, 5-trinitrobenzene (TNB)		5.92×10^{-4} [75]	213	$[M]^-$, $[M-H]^-$	213 →183 (Loss of 30 or NO)
2,4-dinitrotoluene (2,4-DNT)		9.90×10^{-1} [76]	182	$[M]^-$, $[M-H]^-$	82 →165 (Loss of 17 or HO) 182 →152 (Loss of 30 or 30)
1, 3-dinitrobenzene (1,3-DNB)		6.0×10^{-4} [77]	168	$[M]^-$, $[M-H]^-$	168 →138 (Loss of 30 or NO)
2-amino-4, 6-dinitrotoluene		Not available	197	$[M]^-$, $[M-H]^-$	197 →167 (Loss of 30 or NO)
2, 4, 6-trinitrophenylmethylnitramine (Tetryl)		9.98×10^{-3} [78]	287	$[M]^-$, $[M-H]^-$	287 → 270 (Loss of 17 or OH) 286 → 269 (Loss of 17 or OH)

Table 4.3: Summary of the explosive model compounds analysed in negative in mode using the handheld DAPCI ion source.

4.3. 3 Analysis of Nitrobenzene Explosive Mixture using Handheld Portable DAPCI Ion Source

In this experiment a multicomponent stock solution of the explosive mixture consisting of ~10 pg/µL of each component; TNT (Mw 227), TNB (Mw 213), 2, 4-dinitrotoluene (2,4-DNT) (Mw 182), 1, 3-dinitrobenzene (1,3-DNB) (Mw 168), 2-amino-4,6-dinitrotoluene (Mw 197), 2, 4, 6-trinitrophenylmethylnitramine (Tetryl) (Mw 287) in methanol/acetonitrile solution (v/v, 1:1) was utilized. The mixture was analyzed using the handheld DAPCI ion source operated in the negative ion mode. Approximately 1 µL of the matrix solution was spotted onto the paper substrate and analyzed using the commercial ion trap bench-top mass spectrometer. Figure 4.5 shows the mass spectra obtained from the analysis of the nitrobenzene explosive mixture using the handheld DAPCI ion source. Again, as observed for the standard individual nitrobenzene explosive analyte(s), intact radical anions $[M]^-$ and deprotonated molecular $[M-H]^-$ species were observed and each ion was characterized using MS/MS CID to identify each component in the mixture. Insert (i) Figure 4.5 displays the MS/MS CID mass spectrum for the tetryl (Mw 287) molecular anion $[M]^-$ at *m/z* 287, which experiences a neutral loss of -OH upon CID activation to yields the intense peak at *m/z* 270 and that of deprotonated TNT at *m/z* 226. In the case of TNT, the molecular anion $[M]^-$ at *m/z* 227 together with its fragment $[TNT-OH]^-$ at *m/z* 210 and product reaction ion $[TNT+O]^-$ at *m/z* 243 were observed.

Insert (ii) (Figure 4.5) displays the CID product ion mass spectrum of $[TNT+O]^-$ which mainly produces m/z 213 upon collisional activation with a hydroxyl elimination pathway producing $[TNT-H]^-$ at *m/z* 226. Insert (iii), Figure 4.6 shows the MS/MS product ion scan spectrum of 4-amino-2,6-dinitrotoluene (Mw

197) which yields an intense fragment ion at *m/z* 167 due to the loss of NO from the molecular anion $[M]^-$ and a less intense peak at *m/z* 180 due to the loss of OH upon CID activation. Again electron capture dominates for TNT in the negative mode forming *m/z* molecular anion which upon CID activation forms an intense peak at *m/z* 210 due to the loss of OH, and the loss of NO from the molecular anion forms a peak at *m/z* 197 (Appendix C.3). The ability to form radical $[M]^-$ and deprotonated $[M-H]^-$ anions in the negative mode simplifies the resulting mass spectra in the case of mixture analysis performed without prior separation.

Selective *in-situ* detection of nitrobenzene explosives formulations using a custom built handheld DAPCI ion source has been demonstrated. Although the actual mechanism leading to the formation of the oxygen associated adducts is not known at present, the results demonstrate the feasibility of employing ambient air as the DAPCI reagent for selective detection of nitroaromatic explosive formulations without the use of any other solvents or sample workup. The low vapor pressure (Table 1) of most nitroaromatic explosives studied (TNT 4.50 $x10^{-2}$ Torr at room temperature, tetryl 9.98 x 10^{-3} Torr) rules out gas phase ionisation in this case. The nitrobenzene model compounds might have been ionised by the reactant ions formed in the corona discharge; possibly by electron capture in a thermo-chemically controlled chemical sputtering as reported previously [17]. The sputtering step is usually followed by collision of the vapour phase reagent ions with the surface molecules resulting in ion/molecule reactions and electron transfer from the reagent ions to the desorbed nitrobenzene molecules [79]. The results presented herein demonstrate that the handheld DAPCI ion source allows *in-situ* detection of nitroaromatic explosives from surfaces similar to other ambient ionisation methods, such as DESI [17] and LTP [80]. The ability to form radical $[M]^-$ and deprotonated

[M-H]$^-$ anions in the negative mode by electron capture processes simplifies resulting mass spectra in the case of mixture analysis without prior separation. This approach might be particularly valuable for field applications coupled with miniaturized mass spectrometers [49].

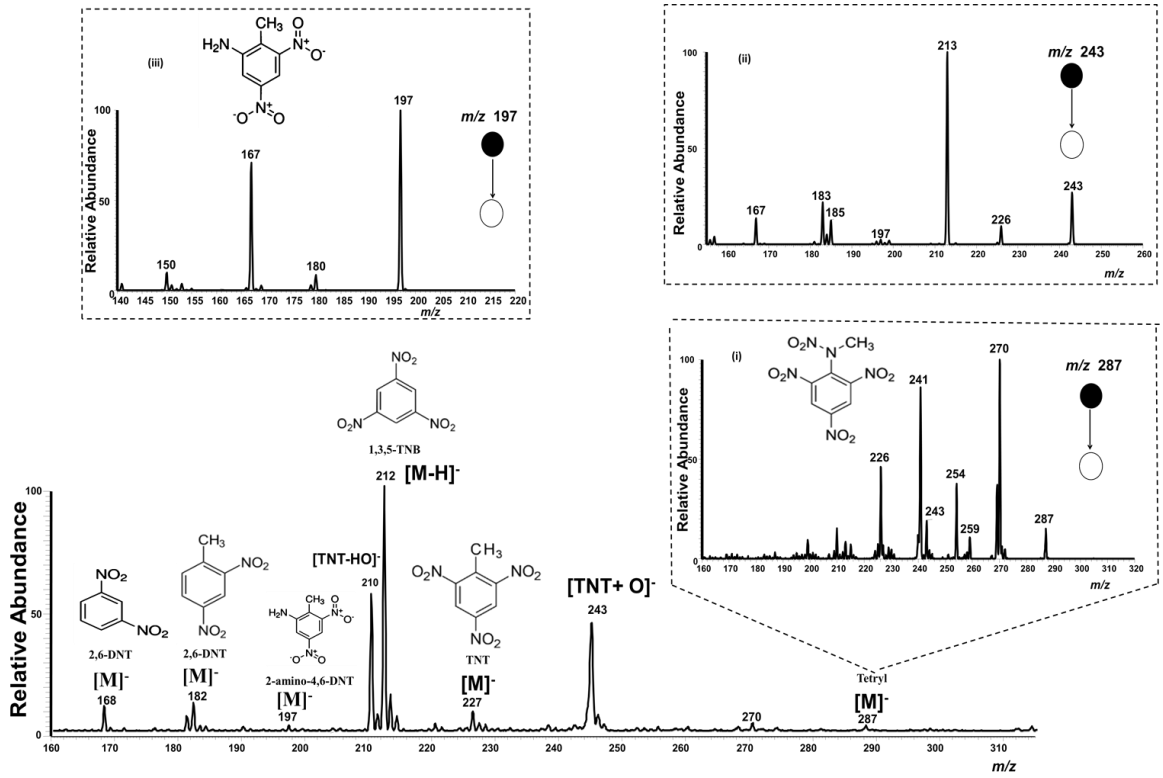


Figure 4.5**:** Negative handheld DAPCI ion mode mass spectrum for a mixture of several explosive model compounds analysed using a bench-top instrument. 10 pg absolute amounts of analyte(s) were contained in the mixture which was deposited onto the surface and ionised in the open environment by application of an electric potential of -2.5 kV in the negative handheld DAPCI ion mode. Most of the nitrobenzene explosive compounds in the mixture gave intact molecular anions [M]$^-$ and deprotonated molecular peaks; 4-amino-2,6-dinitrotoluene (Mw 197), 1,3-dinitrotoluene (Mw 168), 2,6-dinitrotoluene (Mw 182), tetryl (Mw 287). 1, 3, 5-Trinitrotoluene (Mw 213), and TNT (Mw 227) both formed molecular anions [M]$^-$ (at *m/z* 277 and 213 respectively) and deprotonated peaks (at *m/z* 212 and 266). Inserts (i) - (iii) show the MS/MS CID data for; tetryl (*m/z* 287) molecular anion, oxidized TNT product ion at *m/z* 243 and 4-amino-2,6-dinitrotoluene (Mw 197) molecular anion at *m/z* 197 respectively.

4.4.0 Conclusions

In-situ analysis and detection of nitrobenzene explosives absorbed on surfaces using a handheld, portable DAPCI ion source has been demonstrated. Through MS/MS, the handheld DAPCI source has been demonstrated to be an effective method for selective analysis of condensed phase nitrobenzene explosives both individually and in a mixture on surfaces under ambient conditions. From the results shown, it is evident that different nitrobenzene explosive formulations can easily be ionised and detected with a portable, handheld DAPCI ion source coupled to a mass spectrometer. If coupled to a miniaturized mass spectrometer, the ease of use of the handheld DAPCI ion source for *in-situ* experimental analysis should make it a very attractive analytical tool for field applications. That would include homeland security, border control, transportation security, national defence, and forensic investigations and potentially other disciplines such as environmental monitoring where instant and direct detection of a wide range of organic compounds is desirable [81, 82]. Future work will involve on-site analysis and quantification of these compounds in real world scenarios. The results shown here are of interest beyond the nitrobenzene explosives studied. In general they demonstrate the feasibility of *in-situ* analyses using a handheld, portable DAPCI ionisation source operated in open air for "point and shoot" applications with data acquisition in near real time. In the chapter that follows (chapter 3), spray-based ambient ionisation source “paper spray (PS)” is investigated for the *in-situ* analysis and quantification of corrosion inhibitors in both water and petroleum oil samples. Also the direct analysis of metaldehyde, a drinking water pollutant, is presented.

4.5.0 References

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Chapter 5 : *In-situ* Analysis of Water and Petroleum Oil Using Paper Spray Ionisation

5.1 Overview

Paper spray mass spectrometry (PS-MS) provides a direct analysis and identification of long chain aliphatic primary diamine Duomeen® O (*n*-oleyl-1,3–diaminopropane), a corrosion inhibitor in water samples at LODs (<0.1 pg) and has been demonstrated for the first time. No sample preparation using paper spray mass spectrometry (PS-MS) was necessary. The presence of Duomeen® O in water samples was confirmed *via* tandem mass spectrometry using collision-induced dissociation and supported by exact mass measurement and reactive paper spray experiments using an LTQ Orbitrap Exactive instrument. Data shown herein indicate that paper spray ambient ionisation can be readily used as a rapid and robust method for *in-situ* direct analysis of polyamine corrosion inhibitors in an industrial water boiler plant and other related samples in the water treatment industry. This approach was then applied for the analysis of Duomeen® O in three complex water samples including feed water, condensate water, and boiler water, all collected from a large medium pressure (MP) water tube boiler plant, known to be dosed with varying amounts of polyamine and amine corrosion inhibitor components. Polyamine Chemistry is widely used for example in large high pressure (HP) boilers operating in municipal waste and recycling facilities to prevent corrosion of metals. The samples used are from such a facility in a Coventry waste treatment facility, UK which has 3 x 40 tonne / hour boilers operating at 17.5 bar.

Metaldehyde is extensively used worldwide as a contact and systemic molluscicides for controlling slugs and snails in a wide range of agricultural and horticultural crops. Contamination of surface waters due to run-off, coupled with its moderate solubility in water, has led to increased concentration of the molluscicides in surface waters. In addition to the detection of corrosion inhibitors in water, characterization of metaldehyde residues and the effect of the ion types in its quantification in water were investigated, using paper spray mass spectrometry (PS-MS) for the first time. The observed precursor molecular ions (sodiated versus protonated) of metaldehyde were confirmed from tandem mass spectrometry (MS/MS) experiments by studying the fragmentation patterns produced via collision-induced dissociation. Using a commercial linear ion trap mass spectrometer, the signal intensity ratios of the most abundant MS/MS transitions for metaldehyde (177→149 for protonated ion, and 199→67 for sodiated ion) and atrazine (221→179) were found to be linear in the range 0.01 - 5 ng/mL and 0.5 - 50 µg/mL, respectively. Metaldehyde residues were detectable in water samples at low concentration (LOD ~ 0.05 pg/mL using protonated ions) without any pre-concentration/separation steps. The results obtained from this investigation are of particular importance for environmental monitoring and water quality analysis providing a means of rapid screening to ensure safe drinking water.

PS ambient ionisation technique is coupled/integrated to a portable mass spectrometer and applied to the *in-situ* detection of alkyl quaternary ammonium corrosion inhibitors in a complex petroleum oil matrix. The active components of the corrosion inhibitors were identified in oil and confirmed by their fragmentation patterns recorded using tandem mass spectrometry (MS/MS). The cations of alkyl and benzyl-substituted quaternary ammonium salts showed characteristic neutral

losses of C_nH_{2n} (n = carbon number of the longest chain) and $C_7H_{8,}$ respectively. Individual quaternary ammonium compounds were detected at low concentrations (< 1ng/µL) and over a dynamic range of ~5 ppb - 500 ppb. Direct detection of these compounds in complex oil samples without prior sample preparation or pre-concentration was also demonstrated using a home-built miniature mass spectrometer at levels below 1ng/ µL.

5.1.1 Introduction

The addition of corrosion inhibitors to corrosive systems is a well-established preventative approach worldwide [1-4]. Neutralizing agents such as aliphatic and aromatic amines, mono, di- or poly-amines and their salts when added in small amounts to a corrosive water boiler system are known to reduce, slow down or prevent corrosion to metal [5-9]. In agreement with green chemistry aims, new corrosion inhibitor formulations should be less toxic, soluble in aqueous medium, and biodegradable [10-15], especially when they are to be used in portable water transfer systems. Therefore, toxic aromatic amines and their salts should be avoided and replaced with greener long-chain aliphatic mono-, di- or polyamines or their salts [16]. Polyamine corrosion inhibitor formulations are widely used in large high pressure (HP) water tube boiler plants e.g. at refineries, power generating plants, steel works, chemical plants where the operating pressure is > 45 bar. There is a strong need for analytical methods for on-site analysis and quantification of corrosion inhibitor residues in the large HP water tube boiler plant systems and the oil pipeline transportation systems with fast response time, preferably with little or no special sample preparation [17-25]. From such sample(s) the analytical data obtained should be useful in maintaining the appropriate levels of the inhibitor in the

system. This is useful not only for quality control, but in the development of new effective corrosion inhibitors to combat corrosion of the large high pressure (HP) water tube boiler plants and oil pipeline transport lines[26-28].

Currently, different extraction procedures based on solid-phase extraction followed by gas chromatography (GC) or high performance liquid chromatography (HPLC) coupled with mass spectrometry (MS) methods [29-32], have been successfully used in the identification and quantification of the long-chain aliphatic primary poly-diamines in boiler water samples below ppb levels [31, 33, 34]. These analytical methods are reliable, and low limits of detection (LODs) with high specificity and sensitivity can be achieved. However, direct *in-situ* identification and quantification of corrosion inhibitor formulations is not possible at present using GC-MS or HPLC-MS due to the fundamental instrument characteristics, and a large dipole of the poly-diamine [27, 35-37]. To overcome these challenges, poly-diamine corrosion inhibitors are first derivatized and pre-concentrated (using either solid-phase or liquid-liquid extraction) to improve the GC/HPLC detection properties [35, 38-40]. While these analytical methods have proven successful in the analysis of the long chain aliphatic primary poly-diamines corrosion inhibitor formulations in boiler water samples, they can be time consuming. Moreover, these methods are limited by the need for manual transfer of samples to the laboratory before analysis. Therefore, there is a strong interest in rapid screening methods for long chain aliphatic primary poly-diamines inhibitor formulations in large high pressure (HP) water tube boiler plants; that requires no sample preparation, and yet provides specific information regarding the corrosion inhibitor levels. Such methods would have several important applications in the water treatment industry, energy sector, and for environmental monitoring and hygiene [19, 41, 42].

As will be shown in this chapter, ambient ionisation mass spectrometry (AI-MS) combined with tandem mass spectrometry (MS/MS) and exact mass measurements, can meet such criteria [43-45]. In AI-MS, ionisation is performed on unmodified samples in open air and the method is capable of providing almost instantaneous data while minimizing sample preparation. The fact that no sample preparation or prior extraction steps are needed in AI-MS means that experiments are simple, which ultimately reduces the total MS analysis time [46-51]. Some of the most popular AI techniques include desorption electrospray ionisation (DESI[46]), desorption atmospheric pressure chemical ionisation (DAPCI) [52], and direct analysis in real time (DART) [53, 54]. AI-MS shows promise as an analytical tool for *in-situ* applications and has been demonstrated in a variety of fields where timely intervention is highly desirable such as homeland security [55, 56], food safety [57, 58], pharmaceutical and drug development[59].

There are several advantages to using *in-situ* AI methods capable of on-site analysis. The foremost advantage is the provision of data in real-time (or near real-time) at the point of interest allowing key management decisions to be taken in a timely manner. Subsidiary advantages relate to the chain of custody. By effectively "taking the lab to the sample rather than the sample to the lab", the sample integrity is maintained and sampling/handling costs significantly reduced.

Paper spray (PS) ionisation is a relatively new AI-MS method that was introduced to the scientific community in 2010 by Prof Cooks and co-workers at Purdue University [60]. PS mass spectrometry (PS-MS) has been successfully applied in the analysis and quantification of complex molecules, ranging from small organics to large biological molecules including dried blood under ordinary ambient conditions [60, 61]. The use of paper as a substrate material in analytical chemistry

has been demonstrated for several decades and has many advantages such as: high surface area-to-volume ratio, readily available at low-cost, wicks aqueous fluids, biodegradable, lightweight for easy transportation and storage. When using PS, the sample is simply deposited onto a paper substrate (usually a cellulose chromatographic paper) that has been cut to a triangular shape with a fine sharp tip. In a typical PS-MS experiment, the cut paper triangle is wetted with a solvent and charged droplets are emitted from the paper tip when a high DC voltage (± 3 - 5 kV) is applied. Droplet emission occurs presumably by field emission and/or other unidentified mechanisms [62, 63]. Moreover analysis by PS-MS requires little or no sample preparation and the entire experiment can be completed within seconds (<1 minute).

In comparison to other ambient ionisation methods, PS ionisation integrates three analytical procedures: sample collection, separation, and ionisation into a single experimental step making it more attractive for rapid and direct analysis of analyte(s) in complex mixtures. In addition, no nebulizer gases are required and so the technique can be readily used with portable MS in the field [61]. Reactive PS-MS is a variant of the normal PS-MS experiment that incorporates rapid chemical reactions into the PS ionisation process. Reactions occur at the sampling spot concurrently with mass spectra acquisition to improve sensitivity and selectivity for target molecules present in the complex mixtures by doping a reactive reagent into the spray solvent [64-68].

In this chapter PS-MS, a sensitive and selective ionisation analytical method is deployed for the rapid detection and quantification of corrosion inhibitor formulations (i.e. aliphatic long chain primary poly-diamine **(**n-oleyl-1, 3 – diaminopropane (Duomeen® O)), alkyl quaternary ammonium corrosion inhibitor

formulation) and a molluscicide (i.e. metaldeyde) in a variety of complex sample matrices including polyamine and amine mixtures in water collected from a large water tube boiler plant operated at medium pressure (17.5 bar) and quaternary corrosion inhibitor formulations in petroleum oil. Reactive PS-MS is also used in which acetone is doped with the spray solvent to aid in characterization and selective detection of the n-oleyl-1, 3 –diaminopropane (Duomeen® O) corrosion inhibitor formulation from a mixture of polyamines and amines. The samples studied include competitor product A, naylamul S11 and ascamine DW BR1 (mixture of polyamine and amines), and three water samples (feed water, condensate water, and boiler water, pre-drum water, and post-drum water samples) collected from a large high pressure (HP) boiler system at a Coventry waste treatment facility UK that was previously dosed by a six component polyamine and amine corrosion inhibitor.

To successfully characterize and confirm the presence of corrosion inhibitor formulation (i.e. Duomeen® O, analyte(s), alkyl ammonium salts) and metaldehyde in crude complex samples (water and petroleum oil), it was necessary to first analyze a standard with high resolution MS and tandem MS using collision induced dissociation (CID) to determine the molecular formula and structure, respectively. As shown, PS retains the advantages of high sensitivity and specificity typical of MS experiments, plus short (< 1 minute) total analysis times with, no sample pre-treatment; the ability to identify corrosion inhibitor formulations can be achieved readily at trace levels with a limit of detection (LOD) of <0.1 pg (absolute concentration) with acceptable reproducibility (RSD of < 10 %) in a variety of untreated, complex samples.

5.1.2 Detection of Metaldehyde Residues in Water Using PS-MS

Detection and quantification of contaminants in natural water courses is of great importance to ensure safety of drinking water and for the aquatic environment [69-74]. Metaldehyde $(CH_3CHO)_4$ is a cyclic tetramer of acetaldehyde and is widely used globally as a molluscicides for the control of slugs and snails in agriculture to protect crops. Large amounts of metaldehyde residues (from 'slug pellets') become mobilized, especially during periods of rainfall, seeping into reservoirs, rivers and groundwater, from which drinking water is sourced. Although metaldehyde has low toxicity, cases of metaldehyde poisoning and death in both humans and animals have been reported [74-76].

The United States Environmental Protection Agency (EPA) re-registered metaldehyde and required risk-reduction measures to be adopted [77-79]. In Europe, the European Commission has adopted a directive that restricts pesticides levels to 0.1 µg/L in drinking water [80]. Water companies and environmental agencies are under increasing pressure to routinely monitor levels of metaldehyde residues in water courses as part of their legal obligation [81]. As such there is an increasing need to develop effective analytical methods for detecting and quantifying metaldehyde in water samples at the source. In particular *in-situ* monitoring is required to ensure water management practices are based on empirical, up-to-date information which provides a better understanding of competing factors, risk and requirement [82-84].

Rapid analytical methods for *in-situ* analysis of metaldehyde in water, if available, would provide critical information on water quality for water companies and regulators to manage exposures. Quantitative analysis of metaldehyde has been reported using various *ex-situ* methods based on solid-phase extraction [76, 85],

followed by gas chromatography (GC) or high performance liquid chromatography (HPLC) with mass spectrometry (MS) [42, 75, 81, 85-87]. However, each of these analytical methods involves extensive sample preparation including extraction, separation, and derivatisation, resulting in increased cost and time of analysis.

As will be demonstrated in this chapter, ambient ionisation mass spectrometry (AI-MS) combined with tandem mass spectrometry (AI-MS/MS) can overcome such limitations [47, 48, 88]. Experiments were carried out using a commercial benchtop ion trap mass spectrometer coupled with PS ionisation for the *in-situ* rapid detection of metaldehyde in water. The results obtained show that <0.1 pg μL^{-1} of metaldehyde in water placed onto paper can be readily detected. The limit of detection (LOD) is 0.05 pg mL^{-1} and below the permitted minimum EU levels for drinking water. Metaldehyde residues in water samples were identified and confirmed by analysing the fragmentation patterns of metaldehyde in water generated using tandem mass spectrometry (MS/MS).

5.1.3 *In-situ* Analysis of Corrosion Inhibitor Residues in Petroleum Oil Using a Portable Mass Spectrometer with Paper Spray

Corrosion of oil transmission pipelines [89-92] can result in leakage and large scale oil spills that are destructive of the ecosystem and pollute drinking water supplies [93-97]. Corrosion of the oil transmission pipeline is inhibited through addition to the crude petroleum of oil-soluble heterocyclic compounds such as quaternary ammonium salts and ionic liquids [84, 98, 99]. Successful inhibition depends on the amount of inhibitor, and so measurement of inhibitor levels in crude oil is of great interest, especially in long-distance transfer pipelines [11, 100, 101]. Currently, there is no standard method for direct in-field monitoring of residual

levels of corrosion inhibitor [102]. In this chapter ambient ionisation [41, 46, 47, 49, 51, 68, 103] used with miniature portable mass spectrometers [104, 105] is demonstrated as a rapid and efficient method which will allow *in-situ* monitoring of corrosion inhibitors in the oil in transmission pipelines. The PS-MS method is soft (it deposits little internal energy into ions) and amenable to the analysis of small and large molecules ranging from simple organics to large biomolecules. The investigated standard model compound examined included; tetradodecylammonium bromide and benzylhexadecyldimethylammonium chloride which are representative of the active components in many corrosion inhibitor formulations. Both compounds contain long hydrophobic alkyl chains that allow them to dissolve in oil. The results show that <0.1 ng/µL of quaternary ammonium salt in 1 µL oil (e.g., pump oil) placed onto paper can be detected easily using either a commercial benchtop or a home-built miniature mass spectrometer. The concentration (<100 ppb) of the active corrosion inhibitor is well below the reported minimum effective range of concentrations of these inhibitors, which is 50 – 200 ppm [106]. Further, *in-situ* analyte(s) identification and quantification can also be achieved by analysing the fragmentation patterns of the corrosion inhibitors generated using collision induced dissociation (CID) tandem mass spectrometry (MS/MS) [107-110].

5.2.1 Experimental

In all experiments, the sample preparation steps were limited to dilution of standard model compounds in appropriate reagents. For quantification purposes, it was required to spike the solution with an isotopically labelled internal standard, while real samples were analysed directly as supplied without any dilution unless otherwise stated.

5.2.2 Chemicals, Reagents and Materials

All the organic solvents used in the PS-MS experiments (methanol, acetonitrile (HPLC grade) and acetone) were purchased from Mallinckrodt Baker Inc. (Phillipsburg, NJ). The chromatography paper used as PS sample substrate was Grade I cellulose purchased from Whatman (Whatman International Ltd, Maidstone, UK). The standard model compounds; n-oleyl-1, 3-diaminopropane (Duomeen® O), cyclohexylamine, morpholine, diethyl amino ethanol, and the polyamine and amine mixture corrosion inhibitor formulations: (competitor product A, naylamul S11 and ascamine DW BR1), used in this study were supplied by B&V Water Treatment company (Lamport Drive, Heartlands Business Park, Daventry, Northamptonshire, NN11 8YH, UK). Standard solutions (1.0 mg/mL) of cocaine, methamphetamine and amphetamine were obtained from Cerilliant (Round Rock, TX). The crude water samples (i.e. feed water, condensate water and boiler water) were collected from a large high pressure (HP) water tube boiler plant at the Coventry waste treatment facility UK, that was previously dosed by a six component mixture of cyclohexylamine, diethyl amino ethanol, mono ethanol amine, methyl ethyl ketonoxime, Duomeen® O and tallow S 11 corrosion inhibitor formulation. Pure standards of metaldehyde and paraldehyde were purchased from Sigma-Aldrich (UK) as were HPLC grade solvents methanol and formic acid. The deuterium labelled standards, metaldehyde-d_{16} and atrazine-d_5, were purchased from QMX laboratories (Essex, UK). The water samples (Abberton Raw & Chigwell Raw) were supplied by Northumbrian Water (Durham, UK).

For quaternary corrosion inhibitor analysis, pure standard compounds with properties similar to the actives in quaternary ammonium corrosion inhibitors were purchased from Sigma-Aldrich (St. Louis, MO), namely, tetraoctylammonium

bromide, tetradodecylammonium bromide, tetrahexylammonium bromide, tetrabutylammonium hexafluorophosphate, hexadecyltrimethylammonium bromide, benzylhexadecyldimethylammonium chloride, hexadecyltrimethylammonium bromide, and a mixture of alkyldimethylbenzyl ammonium chloride ([C6H5CH2N(CH3)2R]Cl where the alkyl group R is predominantly n-C12H25 but also contains (C14) and (C16) homologs).

5.2.3 Sample Preparation

Sample preparation was reduced to the dilution of the model compounds to the desired concentration while no sample preparation was performed for the raw boiler water and petroleum oil samples. Each model compound was diluted in methanol (HPLC grade) to a desired concentration. From each solution, 2 µL (unless otherwise stated) was deposited using a pipette onto cellulose paper substrate and then analysed using PS-MS. The boiler water sample mixtures (i.e. feed water, condensate water, boiler water), and polyamine and amine mixture (i.e., competitor product A, naylamul S11 and ascamine DW BR1), were used as supplied without any modification or pre-concentration. 2 µL of each sample deposited using a pipet onto cellulose paper substrate analysed using normal PS-MS and *reactive*-PS-MS. Samples were dissolved in methanol to make a stock solution at 1000 ppm. Working solutions were prepared by appropriate serial dilution with methanol/acetonitrile (1:1, v/v).

For quaternary ammonium corrosion inhibitors, an artificial mixture consisting of each of the model compounds at 100 ppb concentration was prepared so that approximately the same ion abundances might be recorded. In order to mimic the oilfield conditions, vacuum pump oil (Inland 19 Petroleum Lubricating oil CAS

Number: 64742- 65-0) was used to dilute the stock solution of the model compounds to 10 ppb concentration and this sample was then analysed without any pre-concentration or purification. Chromatography filter paper used for paper spray was purchased from Whatman (Whatman, no.1, Whatman International Ltd., Maidstone, UK). Methanol/acetonitrile (1:1, v/v) was used as the spray solvent for all the paper spray experiment unless otherwise stated.

5.2.4 Mass Spectrometry Instrumentation

All *ex-situ* experiments were performed using a linear ion trap; (LTQ) mass spectrometer (Thermo Fisher Scientific, San Jose, CA USA), while the *in-situ* experiments were performed using a custom build miniature instrument (Mini 12). The Thermo LTQ mass spectrometer instrument was tuned for optimum detection of the precursor ion of interest, was used under the following instrumental conditions; the temperature of the MS capillary inlet was typically set at 250^{o}C, the tube lens voltage was set at 65 V and the capillary voltage maintained at 15 V in both positive and negative modes, respectively. The PS ion source was placed 3 mm in front of the inlet the LTQ instrument in all the experiments. An electric potential of ±3.5 kV was used for all the PS experiments in both positive and negative mode. It is important to note that in the paper spray experiments no carrier gas is required, instead a plume of ions is generated only with the application of a potential on the paper with the sample and the spray solvent as shown in Figure 5.1.

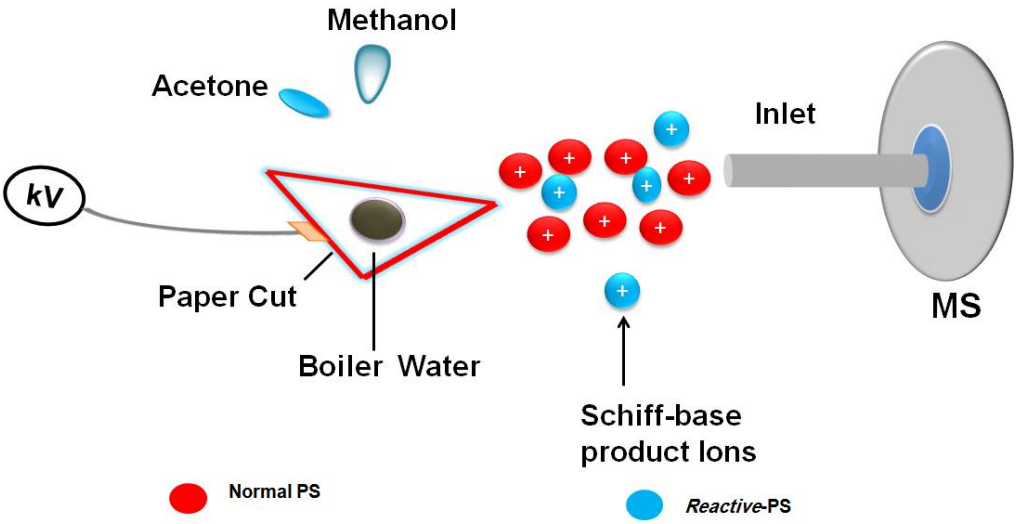


Figure 5.1: Schematic of the typical Paper Spray Mass Spectrometry experimental setup.

Approximately ~2 µL of each sample was deposited on a filter paper surface and analyzed directly without any sample preparation. Tandem mass spectrometry (MS/MS) was used for the structural elucidation and analyte identification was performed on the molecular ions of interest using collision-induced dissociation (CID). An isolation window of 0.1-1.5 Th (mass/charge units) and normalized collision energy of 15-40% (manufacturers unit) was used. Furthermore, the identities of the studied long-chain polyamine and other corrosion inhibitor formulations were confirmed using a high resolution mass measurement Orbitrap mass spectrometer (Exactive, Thermo Fisher Scientific, San Jose, CA USA). The experimental conditions on the Orbitrap were as follows: maximum injection time of 50 ms, two microscans, and activated automatic gain control (AGC).

5.2.5 Paper Spray Mass Spectrometry

A cellulose chromatography paper (Whatman, Maidstone, UK grade I) was used as the paper substrate, and equilateral triangles with ~ 5 mm sides were cut

manually with scissors. The tips of the base angles were cut off and the vertex angle was kept sharp. The paper substrate was held by a copper clip (Figure 5.1) so that the vertex was ~3 mm away from the inlet capillary of the mass spectrometer with an atmospheric pressure interface that transports the spray plume of ionised analyte(s) into the vacuum system of the mass spectrometer for analysis. The sample solution was applied to the paper triangle followed by application of a high voltage. The typical experimental parameters used were as follows: papers spray solvent 10 μL of acetonitrile; the voltage applied to the paper was in the range of + 3.5 kV in positive and – 3.5 kV negative modes. In all experiments (unless noted) the instrument was set to record spectra in the AGC mode for a maximum ion trap injection time of 100 µ seconds and 3 micro scans were combined per spectrum. Figure 5.1 shows the experimental protocol that was followed in all the PS-MS experiments; first a blank spectrum of 10 µL methanol was taken before the sample was applied onto the paper substrate. The analysis was performed in both full MS mode for analyte identification and tandem MS mode for structure elucidation.

5.2.6 Reactive Paper Spray Mass Spectrometry

In the *Reactive*-PS-MS experiment utilizing the Schiff-base reaction, pure acetone was utilized to enhance the selectivity and specificity of the long chain n-oleyl-1, 3-diaminopropane in a variety of water sample matrices (i.e. boiler water, condensate water, and cooling water samples)**.** In this experiment, 10 µL of the pure acetone reagent was added to cellulose paper with long chain **N**-oleyl-1, 3-diaminopropane using a pipette. All the *reactive*-PS-MS experiments were performed using a commercial LTQ instrument (as shown in Figure 5.1) following

the same settings and procedures as used in the normal PS-MS experiment described above.

Samples were dissolved in methanol to make a stock solution of 1000ppm. Working solutions were prepared by appropriate serial dilution with methanol/acetonitrile (1:1, v/v). Acetonitrile and methanol (both HPLC grade) were obtained from Mallinckrodt Baker Inc. (Phillipsburg, NJ). An artificial mixture consisting of each of the model compounds at 100 ppb concentration was prepared so that approximately the same ion abundances might be recorded. In order to mimic the oilfield conditions, vacuum pump oil (Inland 19 Petroleum Lubricating oil CAS Number: 64742-65-0) was used to dilute the stock solution of the model compounds to 10 ppb concentration and this sample was then analysed without any pre-concentration or purification. Chromatography filter paper used for paper spray was purchased from Whatman (Whatman, no.1, Whatman International Ltd., Maidstone, UK). Pure methanol and methanol/acetonitrile (1:1, v/v) was used as the spray solvent for all the paper spray experiment unless otherwise stated.

5.2.7 Determination of the Detection Limits

The limit of detection (LOD) of analyte(s) studied was determined as the concentration that produces a signal more than three times greater than the standard deviation plus the mean value of the blank runs, in MS/MS mode using a commercial linear ion trap mass spectrometer (LTQ) instrument. For Duoamine O, the signal intensity ratios of the most abundant MS/MS transitions (at *m/z* 325.5 → 308) were found to be linear (regression parameters: $y = 0.0056x + 0.001234$, with R^2 value 0.999; (Appendix D.2.) in the range of absolute amounts from 0.1 to 1000 ppb and showed good reproducibility (relative standard deviation, RSD < 10 % for 1

pg samples deposited on the paper substrate). The Duomeen® O showed a limit of detection (LOD) of 0.1 pg (absolute concentration) when analysed using PS-MS. While the limit of detection (LOD) of metaldyne was determined as the concentration that produces a signal more than three times greater than the standard deviation plus the mean value of the blank (in MS/MS mode). Using a commercial linear ion trap mass spectrometer, the detection limits of metaldehyde using PS ionisation was determined as ~0.05 pg/mL.

The detection limits of the four quaternary ammonium model compounds in both neat solution and oil matrix were determined to be in the low ppb levels. Using the miniature ion trap (Mini 12), the detection limits were ca. 10 times higher than those value obtained by commercial instruments, as summarized in Table 5.3. When quantitatively analysing ammonium salt (tetraoctylammonium bromide) in oils, the calibration curve was obtained by using another ammonium salt (tetraheptylammonium bromide, 250 ppb) as internal standard. The signal intensity ratios of the most abundant MS/MS transitions were found to be linear in the range from 5 ppb to 500 ppb. ($y = 0.0045x + 0.00141$, $R^2 = 0.9973$, as shown in Appendix E (Appendix E.8). The measurements within this range had a relative standard deviation of <10% when three replicates were taken.

5.2.8 *In-situ* analysis Corrosion Inhibitors in oil Using Paper Spray Ionisation with a Miniature Mass Spectrometer

A paper spray ion source was interfaced, as shown in Figure 5.2, to a miniature mass spectrometer the Mini 12.0, which was built and characterized at Purdue University [111]. The mass analysis system, the vacuum system, the control system and the detector are all integrated into a shoe-box sized aluminium box. The

overall instrument uses 65 W average power and weighs 15 kg. The mass analyser is a rectilinear ion trap (RIT) [112, 113], operating at a frequency of 1 MHz enclosed in a stainless steel manifold of 470 cm^3 volume[113]. As a result of its simplified geometry and pressure tolerance, RITs have many advantages as miniature mass analysers as is evident in earlier applications [113]. The capability for tandem mass spectrometry is especially valuable in enhancing the sensitivity and specificity of mixture analysis. The operating pressure range was in the range $1x10^{-5}$ Torr to ca. $5x10^{-2}$ Torr, with mass analysis scans being performed in the lower range of pressures.

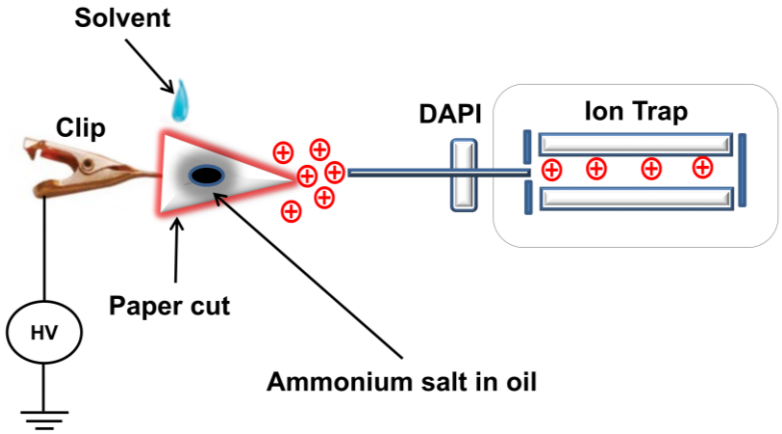


Figure 5.2: Paper spray mass spectrometry for *in-situ* analysis of corrosion inhibitors in oil using a miniature mass spectrometer.

5.2.9.1 Interface to the Mini 12.0 Mass Spectrometer

To achieve an adequate vacuum, a discontinuous atmospheric pressure interface (DAPI) [114-116] was used to directly introduce ions and the accompanying ambient air into the mass analyser from the ambient environment (Figure 5.2). The pressure rises on sample introduction but falls again to levels suitable for mass analysis when the interface is closed. Unlike the conventional

continuous ion introduction technique, DAPI admits discrete pulses of ion/air mixture to reduce the gas load on the pumps. In each sampling period the DAPI is opened for 10-20 ms under the control of a pulse valve. During this period, ions are pulsed into the vacuum system for subsequent analysis. After the DAPI is closed; the neutral gas is pumped away so that the trapped ions can be mass analysed. DAPI has been used widely in miniature mass spectrometers [117].

5.2.9.2 Paper spray ionisation for *in-situ* analysis

The paper spray ion source was held in front of the Mini 12.0 mass spectrometer as shown in Figure 5.2, to achieve rapid *in-situ* analysis of untreated complex mixtures. Results from the *in-situ* experiment using a miniature mass spectrometer were compared with the results from a typical benchtop commercial instrument operating in a typical lab setting.

5.2.10 Tandem Mass Spectrometry Experiment

Mass-selected ions were fragmented through energetic collisions with neutral gas molecules using collision-induced dissociation (CID) in the Mini 12.0 instrument [118, 119]. After the ions had been introduced by opening the DAPI valve for 15 ms, and 850 ms cooling time was provided to restore the vacuum before ion isolation. A broadband stored waveform inverse Fourier transform (SWIFT) signal from 10 kHz to 500 kHz with a notch between 97 kHz and 105 kHz was applied to the x electrodes of the RIT at an amplitude of 3.5 V_{p-p} (peak to peak voltage) for 175 ms to isolate the precursor ions of interest (the experiment was done at a Mathieu parameter q_z value of 0.185 for each ion of interest and the RF amplitude was

appropriately set to place each ion at this value) [118, 120]. To perform CID, an AC signal of 0.45 V at a frequency of 102 kHz was then applied to the x electrodes of the RIT (rectilinear ion trap) for 40 ms after the isolation step [118]. The AC excitation signal was ramped from 1.3 V_{p-p} to 6.6 V_{p-p} at 1000 MHz for resonance ejection while the RF amplitude was ramped from 1 kV_{p-p} to 5 kV_{p-p} at 1 MHz in the acquisition time segment [121].

5.3.0 Results and Discussion

PS-MS analytical method was utilised in the direct identification, structure characterization, and confirmation of the presence of long chain n-oleyl-1, 3-diaminopropane (Duomeen® O) corrosion inhibitor in water samples using chemical reactions, PS-MS or M/MS, and exact mass measurement. The characterization of purified Duomeen® O samples is first presented, followed by quantitative/analytical performance measurements, and finally the analysis of a variety of complex water boiler samples collected from large high pressure (HP) water tube boiler plant (Coventry Waste Treatment facility UK). The long chain Duomeen® O corrosion inhibitor formulation in crude water samples were chosen for the study because its identification and quantification is essential in the optimization of the corrosive system [9, 14, 36], and current efforts have focused on developing new, green, and efficient corrosion inhibitors for water treatment plants [101, 122, 123]. There is also the need to monitor the level of residual corrosion inhibitors to prevent run away reactions. Water transfer pipelines are often carbonated to remove dissolved carbon dioxide species, but the process in turn generates carbonic acid that leads to reduced pH and consequently corrosion. Corrosion inhibitor formulations when added in

small amounts to a corrosive water boiler system neutralize the carbonic acid and bring the pH to a normal value.

5.3.1.0 Analysis and Characterization of Duomeen® O in Water using PS-MS in the Positive Ion Mode

The positive ion PS-MS molecular analysis of Duomeen® O, using 2 µL samples deposited on the chromatography paper triangle was achieved after the application of 10 µL of methanol as the PS spray solvent. The resultant mass spectrum is as shown in Figure 5.3, which is dominated by intact protonated molecular ion $[M+H]^+$ at *m/z* 325 in the mass range of 100-1000 Da, with little or no fragmentation (Figure 5.3 (a)). The insert (i), in Figure 5.3 a shows the isotopic distribution at *m/z* 325, and the high proton affinity of n-oleyl-1, 3-diaminopropane (Duomeen® O) allows for its protonation. The remarkable absence of signal due to the paper spray ionisation background is consistent with the high proton affinities of diamine compounds, a well-known ionisation feature of many chemical ionisation methods.

5.3.1.1 Structure characterization and confirmation of Duomeen® O

Tandem MS via multi-stage CID was employed for the initial structural characterization of the intact protonated $[M+H]^+$, Duomeen® O cation at *m/z* 325. The insert (iii) in Figure 5.3 shows the product ion scan MS^2 mass spectrum obtained in the positive ion mode using PS-MS where the CID dissociation leads to a single fragment ion at *m/z* 308 owing to ammonia (*MW* 17 Da) neutral loss as a result of heterolytic cleavage of the low energy C-H-NH_2 bond. The stability and abundance of the product ion allows three stage (MS^3) tandem MS experiments to be performed. In this particular case, CID of the product ion at *m/z* 308 yielded further fragment

ions at *m/z* 280 through the loss of ethylene (*MW* 28 Da) neutral molecule as shown in insert (iii) Figure 5.3 a.

With molecular weight of 324.6 Da, a major concern about Duomeen O in paper spray was the actual ion type generated (i.e., protonated or radical molecular cation). Nominal mass measurement produced 325.5 Da as the molecular ion (Figure 5.3 a). The MS/MS experiment described above was useful but further verification was needed to confirm the structure of this long chain C_8- Duomeen® O compound. For this, tandem MS was combined with exact mass measurements, which provided the chemical formula assignment in the Xcallibar 3.1 software. The use of 50,000 resolution and lock mass proved to be sufficient to determine the molecular formula of Duomeen® O with error considerably below 1 ppm (Figure 5.3 b).

The proposed molecular formula based on the exact mass measurement confirmed that the detected long chain Duomeen® O formed a protonated molecule $[M+H]^+$ upon ionisation by paper spray ionisation - exact mass of CID fragments and neutral loss (insert (iv), Figure 5.3 (b)) all confirm this assignment which is consistent with the CID data interpretation described in insert (iii) Figure 5.3 (a).

Other corrosion inhibitor formulation model compounds analysed by the PS-MS method included: cycloxylamine (*MW* 99), morpholine (*MW* 87), and dethyl amino ethanol (*MW* 117).These compounds also gave intact protonated molecules $[M+H]^+$, and their identities were confirmed using their MS/MS CID fragmentation patterns (see Appendix D.1 for the mass spectra)

The Duomeen® O showed a limit of detection (LOD) of 0.1 pg (absolute concentration) when analysed using PS-MS. The LOD was determined as the concentration that produces a signal more than three times greater than the standard

deviation plus the mean value of the blank, in MS/MS mode. The signal intensity ratios of the most abundant MS/MS transitions (at *m/z* 325.5 → 308) were found to be linear (regression parameters: $y = 0.0056x + 0.001234$, with R^2 value 0.999; for the calibration curve see Appendix D (Appendix D.2) in the range of absolute amounts from 0.1 to 1000 ppb and showed good reproducibility (relative standard deviation, RSD < 10 % for 1 pg samples deposited on the paper substrate).

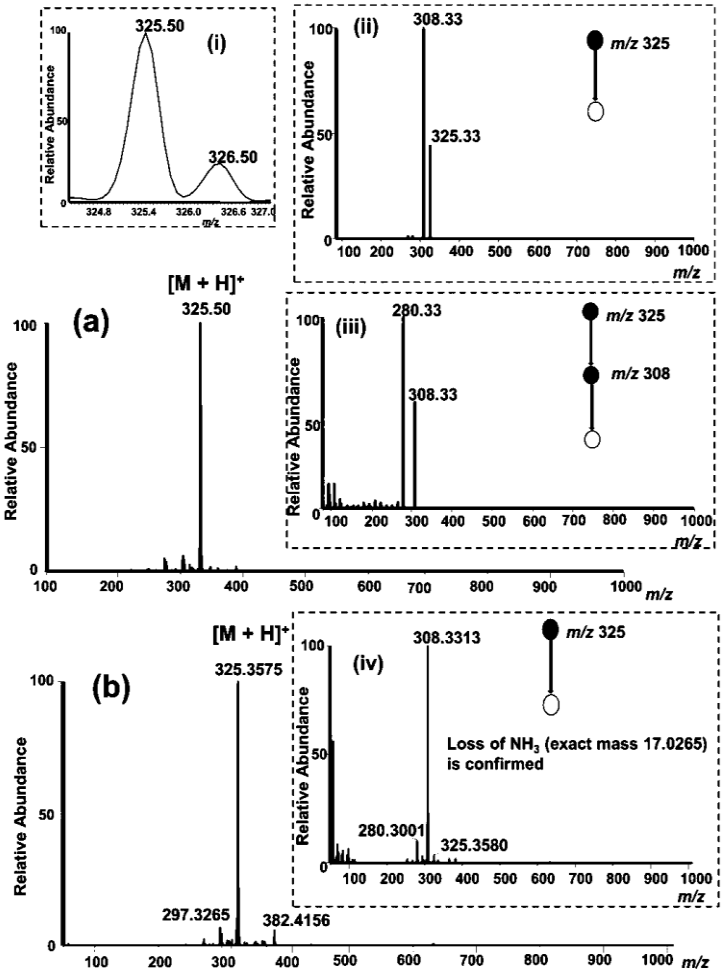


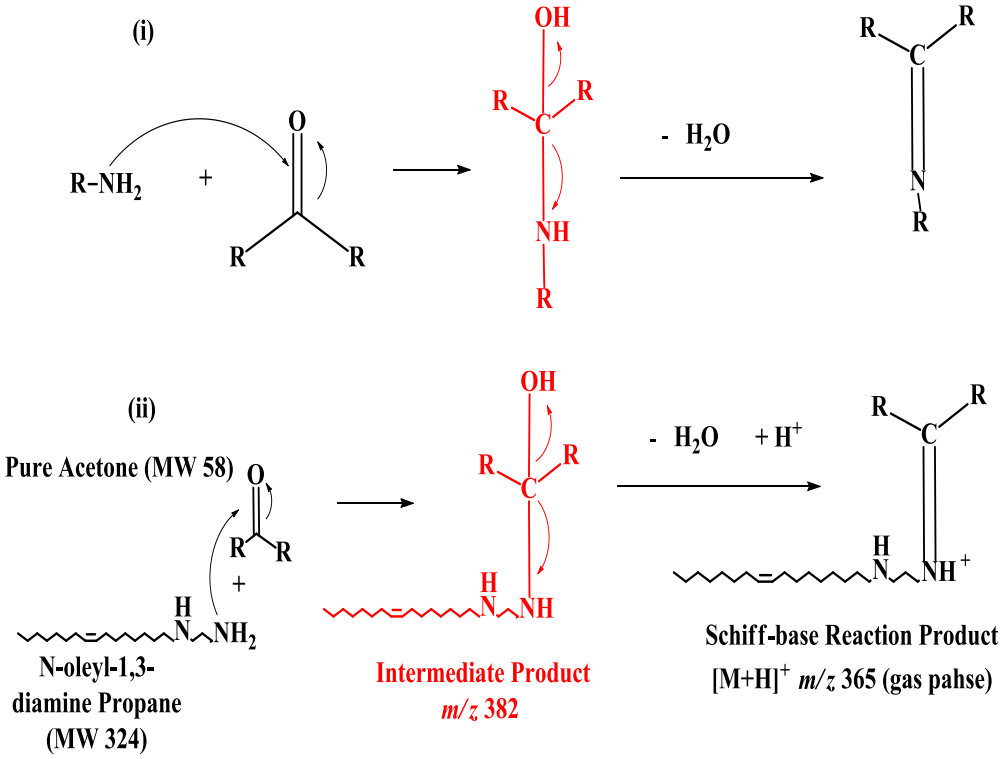
Figure 5.3: Positive ion mode paper spray mass spectrum for Duomeen® O corrosion inhibitor model compound analysed using a bench-top ion trap mass spectrometer. Absolute amounts of analyte were spotted onto filter paper and ionised in the open air by application of an electric potential, 2 µL, *viz* 10 ppb. a) Duomeen® O (Mw 324) in methanol solution b) exact mass measurement of Duomeen® O. Insert (i) shows the isotopic distribution of the Duomeen® O protonated molecular ion [M+H]+ at *m/z* 325, and inserts (ii)-(iii) show the MS/MS CID data for the selected ions. Insert (iv) shows the corresponding exact mass MS/MS CID data

5.3.1.2 *Reactive*-PS-MS: Duomeen® O detection using Schiff-base reaction with acetone

In addition to exploring the direct detection of Duomeen® O using PS ionisation, chemical reactions that form stable adducts can be used in conjunction with PS-MS to enhance the selectivity and detection of analyte(s) in complex mixtures. As such, experiments of this type (reactive-PS-MS) were employed in this study to improve the analysis of Duomeen® O in complex water samples. 10 µL of acetone was spotted *in-situ* onto the paper simultaneously with application of 10 µL methanol solvent as shown in Figure 5.1. Intense mass spectra containing protonated molecular ion [M+H] of Duomeen® O at *m/z* 325 were observed (Figure 5.4 (a)) when only methanol was applied on a filter paper to which Duomeen® O had previously been applied. In contrast, applying acetone in tandem with methanol resulted in a completely different mass spectrum (Figure 5.4 (c)) where the nucleophilic attachment of the carbonyl group in acetone by the primary amine group in Duomeen® O yielded a reaction product with MW 364 Da and concomitant loss of water (Scheme (5.1). The protonated ion of the reaction product is subsequently detected at *m/z* 365. Collisional activation of the ion at *m/z* 365 in CID affords product ions *m/z* 322 (minor) and *m/z* 294 (major) through sequential elimination of ethenamine (*MW* 43 Da) and –ethylene (*MW* 28 Da), respectively as shown in Figure 5.4 (d). This reactive PS experiment provides reliable complementary chemical information which facilitates long chain aliphatic polydiamine and amine corrosion inhibitor formulation identification in complex matrices with enhanced selectivity.

The introduction of reagents in normal PS-MS experiments produce selective detection; when used in combination with tandem MS, this approach

provides the confirmation needed to identify the presence of a particular substance. From these experiments, two reactions occurred on the surface in open air: 1) the non-specific proton transfer reaction forming protonated molecules $[M+H]^+$ (Figure 5.4 (a), and 2) the Schiff-base reaction (Figure 5.4 (b)). It is interesting to note that this condensation reaction between acetone and the amine proceeded rapidly (in less than 5 seconds) to enable analysis in real time. This reaction time scale is consistent with accelerated reaction rates observed for thin film/charged micro-droplet reaction conditions [124, 125].



R: alkyl or aryl group.

Scheme 5.1: Schiff-base Condensation Reaction of the Primary Amines; (i) Nucleophilic reaction between the primary amine and ketone, (ii)Reaction between Duomeen® O (n-oleyl-1,3-diamine propane) (MW 324) and acetone in gas phase under ambient conditions using *Reactive*-PS-MS.

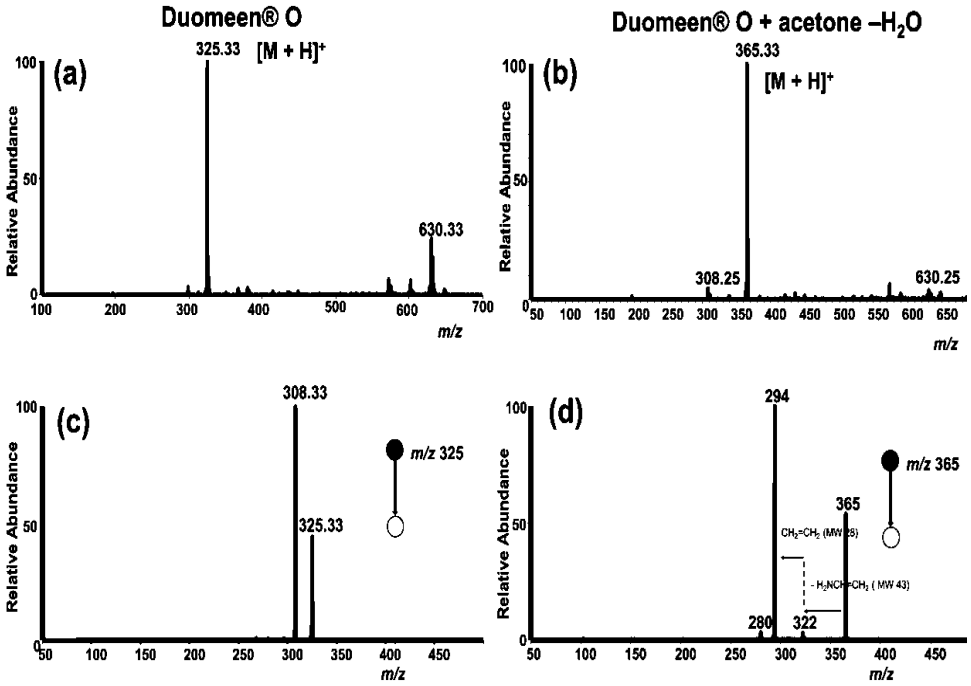


Figure 5.4: Positive ion mode *reactive*-PS mass spectrum Duomeen® O analysed using a bench-top instrument: (a) and (b) shows the typical Duomeen® O mass spectrum analysed without the acetone reagent and MS/MS CID data respectively. While b) and d) show the product of Duomeen® O reaction with acetone detected in open air.

Paper spray ionisation is a particularly simple ambient ionisation technique which can be employed in the field to measure trace constituents of complex mixtures. Although analysis in MS/MS mode adequately removes matrix effects, a decision needs to be made as to what analyte ion within the mixture should be subjected to collisional activation. In this respect, preforming real time chemical reactions onsite will offer an efficient means to eliminate unrelated matrix ions. The generation of a charged product is expected to improve ionisation efficiency in a process once known as ‘reverse derivatisation' [65]. The combined derivatisation/ionisation process is tested in this study for the analysis of Duomeen® O corrosion inhibitor in boiler water samples. As such both ionisation efficiency and molecular selectivity can be improved by chemical derivatisation such as the Schiff base reaction.

5.3.1.3 Direct analysis of Duomeen® O in a Mixture of polyamine corrosion inhibitors Using PS-MS

Direct analysis of the long chain Duomeen® O in complex polyamine and amine mixtures using PS-MS was investigated without any sample preparation. Polyamine and amine complex mixtures including competitor product A, naylamul S11, and acsamine DW BRI were analysed as supplied without further pre-treatment. 2 µL from each sample was deposited onto the paper triangle and analysed using a commercial benchtop mass spectrometer in positive ion mode as described in Figure 5.1. Figure 5.5 (a) shows the recorded mass spectrum for the competitor product A (polyamine and amine mixture) (mass range 200-500) using only methanol as the PS spray solvent. Intense protonated molecular ions of Duomeen® O $[M+H]^+$ at *m/z* 325 were observed, and confirmed by MS/MS CID experiments (insert (i) in Figure 5.5). Two unidentified peaks at *m/z* 337 and 351 were also observed, and MS/MS experiments (inserts (ii and iii), Figure 5.5) showed that they are unrelated to Duomeen® O. This decision was supported by reactive paper spray experiments in which only the peak corresponding to Duomeen O (*m/z* 325) was observed to be affected by the presence of acetone, with the concomitant appearance of an ion at *m/z* 365 (Figure 5.5 (b)). This product ion has previously been identified as coming from a reaction between acetone and Duomeen O (Figure 5.4 (b)) using purified samples. Similarly, the remaining polyamine and amine corrosion inhibitor mixtures (i.e. naylamul S11, and ascameen) were analysed using PS-MS and Duomeen® O was detected and characterized (Appendix D.3).

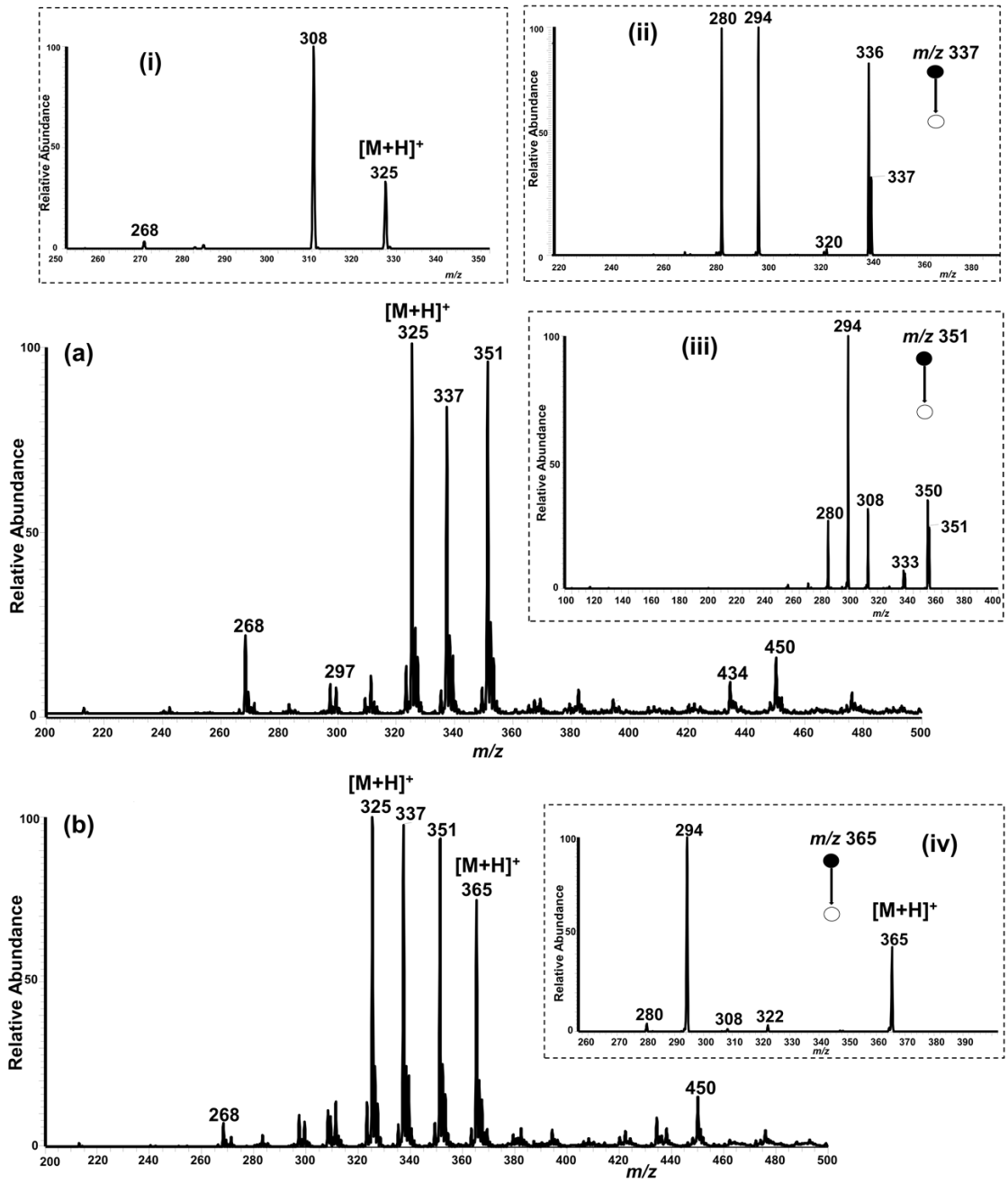


Figure 5.5: Positive ion mode paper mass spectrum for polyamine and amine corrosion inhibitor formulation complex mixture (competitor product A) analysed using a benchtop mass spectrometer. (a) Mass spectrum of competitor product A corrosion inhibitor mixture analysed without acetone reagent. 2 µL of the corrosion inhibitor mixtures was deposited onto the surface and ionised and analysed in the open air by application of an electric potential of + 3.5 kV positive ion mode. Insert (i)-(iii) are the MS/MS CID mass spectra for the *m/z* 325, *m/z* 337, *m/z* 351 respectively, **(**b) Mass spectrum of competitor product A corrosion inhibitor mixture analysed with acetone reagent. The protonated ion of the reaction product is subsequently detected at *m/z* 365. Insert (iv) is the MS/MS CID mass spectra for the *m/z* 365.

The ability to detect and characterize Duomeen® O in a variety of different raw crude boiler water samples collected from a water tube boiler plant waste treatment facility (Coventry UK) has been demonstrated. In this experiment 2 µL from each sample was deposited on the paper substrate and analysed using PS-MS. Figure 5.6 shows the recorded mass spectra for (a) condensate water, (b) feed water, and (c) boiler water. Moderately intense protonated molecular ions $[M+H]^+$ of Duomeen® O were observed and confirmed using MS/MS CID data as shown in Figure 5.6, inserts (i)-(iii) in condensate, feed and boiler water samples. The identification of the Duomeen® O molecule in a variety of crude water samples collected from a large high pressure (HP) water tube boiler plant demonstrate the utility of the PS-MS method for direct, rapid screening with little or no sample preparation. It is important to note that other protonated molecules for amine compounds such as cyclohexylamine (MW 99), diethyl amino ethanol (MW 117), were also detected and confirmed using MS/MS CID data (Appendix D.3) in the feed water and boiler water at *m/z* 100, 118 (Figures 5.6 b and c).

One advantage of ambient ionisation methods is their compatibility with high-throughput rapid screening. To implement successful screening experiments, the analyte(s) of interest need to be carefully evaluated with respect to the matrix due to possible complications of ionisation suppression and isobaric ion interference. In Figure 5.6 Duomeen® O was observed among the low abundant ions detected in the full mass spectra from the water samples (Figure 5.6). The same analyte concentrations were sensitively detected in MS/MS mode in which matrix effects are completely eliminated. As demonstrated in other PS-MS experiments [45, 48], the porous cellulose paper substrate used for ionisation reduces/filters a large proportion

of the particulate present in complex samples and reduces ion suppression effects without extensive sample preparation.

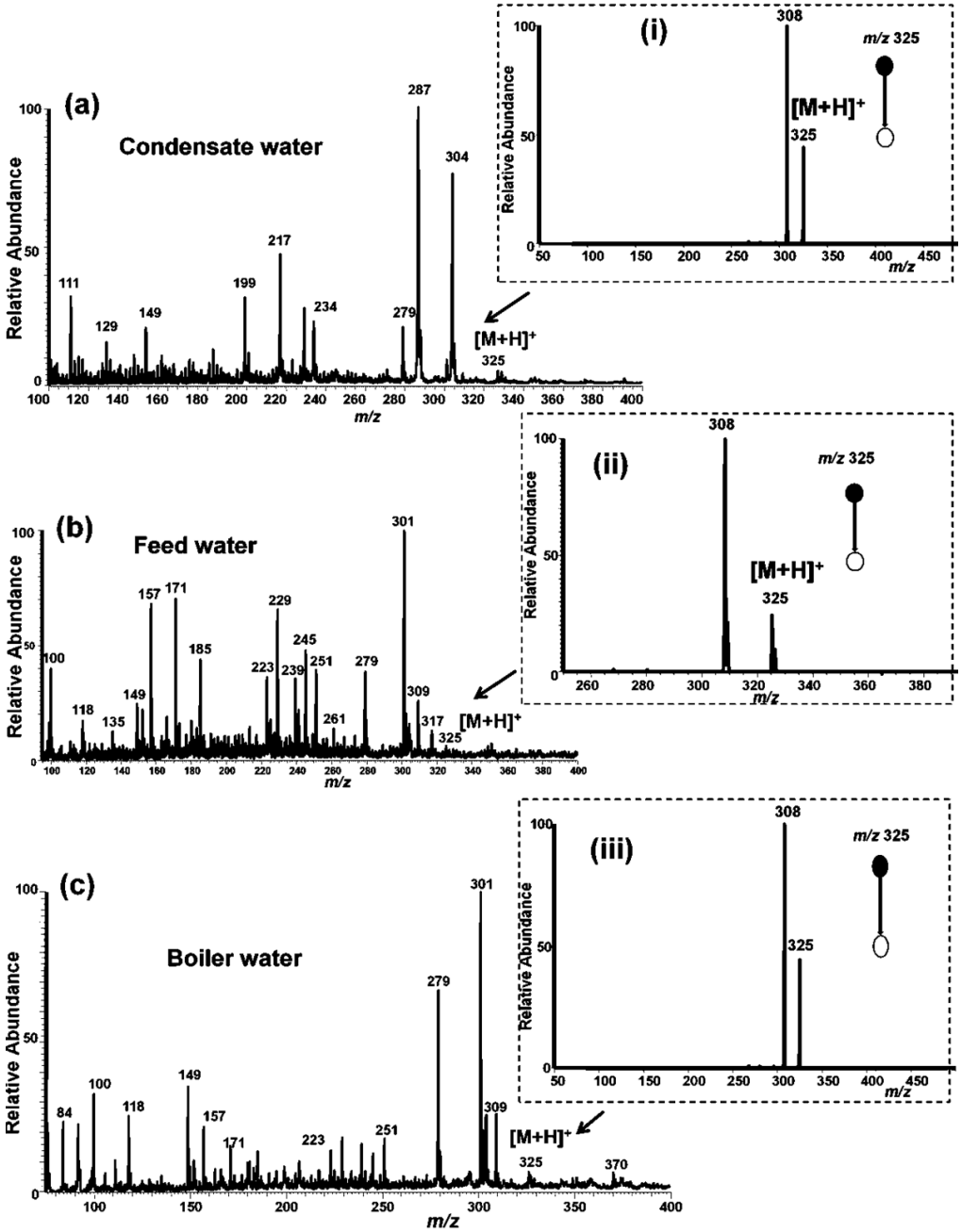


Figure 5.6: Positive ion mode paper spray mass spectrum for rapid detection of Duomeen® O corrosion inhibitor boiler system water samples: (a) condensate water, (b) feed water, (c) boiler water. 2 µL of the sample was deposited onto the surface and ionised in the open environment by application of an electric potential of + 3.5 kV positive ion mode. Insert (i)-(iii) are the MS/MS CID mass spectra for the protonated Duomeen® O at *m/z* 325 detection from each sample.

Direct analysis of Duomeen® O at very low concentrations (<0.5 pg absolute) in complex mixtures has been demonstrated using paper spray mass spectrometry. The MS/MS experiments, complimented by the reactive PS-MS method, provide a powerful means of qualitative analysis with little or no sample preparation. As demonstrated in this study, either tandem MS or reactive PS-MS can be used to analyse Duomeen® O in complex mixtures. Since quantification was carried out in MS/MS mode, it was required to establish the fragmentation pattern of Duomeen® O in collision-induced dissociation experiments. For complex mixtures, it is often difficult to identify species of interest; to improve the efficacy of the identification process for Duomeen® O, a reactive paper spray approach is necessary in which reactive reagents/solvents such as acetone is added to the methanol/water spray solvent. Any mass shifts observed after the *in-situ* reaction with acetone signified the presence of an amine functional group, potentially from Duomeen® O analyte in water, which can then be quantified in subsequent MS/MS experiments.

5.3.2.0 Direct Detection of Metaldehyde in Water using PS-MS

Metaldehyde is an organic compound with the formula $(CH_3CHO)_4$. It is commonly used as a molluscide (pesticide) against slugs, snails, and other gastropods. It is the cyclic tetramer of acetaldehyde. Paper spray mass spectrometry method was applied to the analysis of metaldehyde in water samples. Experiments were carried out using a commercial benchtop ion trap mass spectrometer coupled with PS ionisation as shown in Figure 5.1. The sample preparation steps were limited to dilution of standard model compounds in deionised water. For quantification purposes, it was required to spike the solution with an isotopically labelled internal standard. The results show that <0.1 pg μL^{-1} of metaldehyde in water placed onto

paper can be readily detected. The limit of detection (LOD) is 0.05 pg mL^{-1} and below the permitted minimum EU levels for drinking water. We took advantage of the fact that the cyclic nature of metaldehyde can encourage the inclusion of different ions (H^+, Na^+ and NH_4^+) to enable the formation of different metaldehyde ion types when analysed using different spray solvents. When collisionally activated each ion type ($[M+H]^+$ versus $[M+Na]^+$ versus $[M+NH_4]^+$) dissociates through unique pathways leading to the generation of unique product ions. These fragmentation patterns were fully characterized through tandem mass spectrometry (MS/MS) experiments using neutral and acidified metaldehyde water samples.

5.3.2.1 Characterization of Metaldehyde Detection using PS-MS

The detection of residues of metaldehyde in water samples in the pbb range (0.05 - 5 ppb) using paper spray mass spectrometry is demonstrated for the first time. Figure 5.7 shows the mass spectra of metaldehyde (*MW* 176) obtained in positive ion mode using paper spray ionisation with methanol as the spray solvent. A dominant sodium adduct ion $[M+Na]^+$ of metaldehyde at *m/z* 199 and a less intense ammonium adduct ion $[M+NH_4]^+$ at *m/z* 194 were observed (Figure 5.7 (a)). Insert (i) in Figure 5.7 (a) shows the isotopic distribution of the metaldehyde sodiated adduct $[M+Na]^+$ at *m/z* 199. To confirm the identity of the molecular sodiated ions $[M+Na]^+$ attributed to *m/z* 199, product ion MS/MS spectra were recorded using collision-induced dissociation (CID). The result from this experiment is as shown in insert (ii), Figure 5.7 (a), which indicates that upon CID activation the ion at *m/z* 199 yields a predominant fragment ion at *m/z* 67. This ion corresponds to sodiated acetaldehyde (*MW* 44) formed from the sequential loss of neutral dimer (*MW* 88) and monomer (*MW* 44) of acetaldehyde. Indeed, the intermediate fragment ion formed after the

dissociation of the acetaldehyde dimer is observed at *m/z* 111, followed by the elimination of the monomer. A competing fragmentation pathway to the loss of the dimeric acetaldehyde was detected to correspond to the elimination of water (18 Da) molecule to give a less intense fragment ion peak at *m/z* 181. The less intense ammoniated molecular peak observed at *m/z* 194 was also confirmed via CID (see Appendix D.4). Upon CID activation the ion at *m/z* 194 yields a fragment through sequential loss of two water (18 Da) molecules, yielding an intense product ions at *m/z* 176 and *m/z* 158 (major).

The sodiated molecular $[M+Na]^+$ ion fragmentation assignment discussed above was further confirmed using deuterated metaldehyde-d_{16} (*MW* 192) as the sample. Here too, a dominant sodiated molecular ion $[M+Na]^+$ at *m/z* 215 was observed demonstrating that the adduction with Na^+ ion was unaffected by isotopic substitution (Figure 5.7 (b)). These sodium adducts were formed with relatively low internal energy as indicated by the fact that no associated fragmentation is observed in the full mass spectrum (Figure 5.7). Insert (iii), Figure 5.7 b shows the CID data of the intact metaldehyde-d_{16} sodiated molecular $[M+Na]^+$ ion at *m/z* 215, which upon CID activation dissociates yielding a more intense fragment ion at *m/z* 71 $[CD_3CDO + Na]$ via sequential elimination of dimer (96 Da) and monomer (48 Da) of acetaldehyde-d_4 without H/D scrambling as shown in insert (iv), Figure 5.7 (b). The stability and abundance of the precursor $[M+Na]^+$ molecular ion from metaldehyde-d_{16} allowed multi-stage MS/MS/MS experiments to be performed and the result is as shown in insert (v), Figure 5.7 (b), which unambiguously confirms the source of the *m/z* 71 product ion. Like metaldehyde, the deuterated metaldehyde-d_{16} - species also formed adducts with ammonium ions at *m/z* 210.

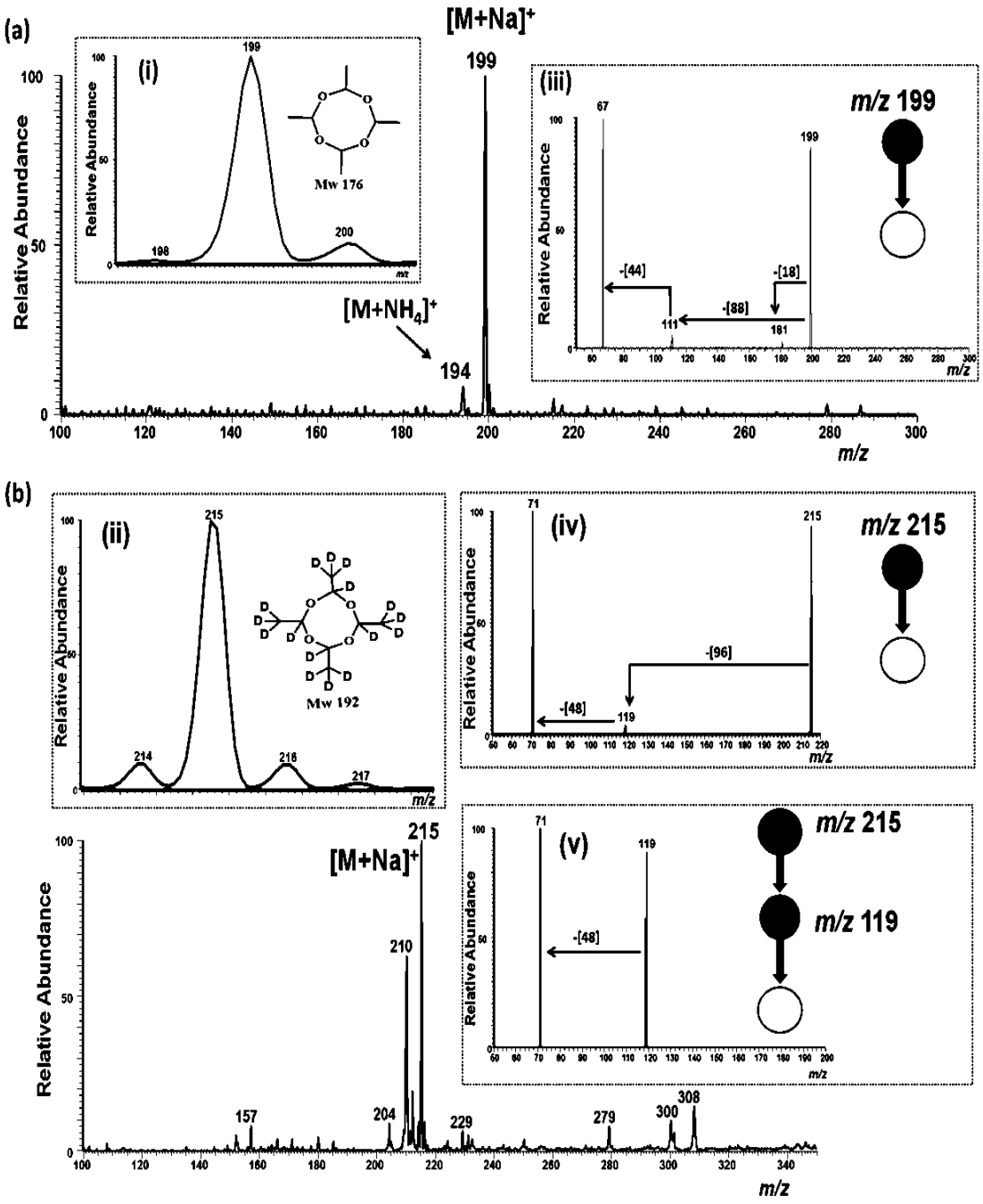


Figure 5.7: Positive ion mode paper spray mass spectrum of metaldehyde recorded using a bench-top ion trap mass spectrometer. 5 μg of the analyte in 1 μL methanol solution was spotted onto filter paper and ionised in air by application of a positive electric potential (3.5 kV) using methanol as the paper spray solvent. (a) The sodiated molecular ion $[M+Na]^+$ peak of metaldehyde (*MW* 176) in methanol produced the dominant ion signal intensity (*m/z* 199), and (b) Sodiated molecular ion $[M+Na]^+$ of deuterated metaldehyde-d_{16} (*MW* 192) in methanol produced the dominant ion peak, analysed using PS-MS. Inserts (i)-(ii) show the isotopic distribution of the metaldehyde and metadehyde-d_{16} sodiated $[M+Na]^+$ ion adducts at *m/z* 199 and 215 respectively. Inserts (iii) -(v) show the tandem MS CID data for the selected ions of metaldehyde and metadehyde-d_{16}.

5.3.2.2 Analysis of Protonated Metaldehyde Species Using PS-MS

From the results discussed above, it can be hypothesized that the sodium $[Na]^+$ and the ammonium $[NH_4]^+$ ions masked/suppressed the protonation of metaldehyde. To suppress the cationisation adducts (i.e. $[Na]^+$ and $[NH_4]^+$) and enhance protonation of metaldehyde, the paper spray solvent was optimized by adding acidified water (0.1% formic acid) to the methanol solvent giving MeOH:(H_2O + 0.1% formic acid) (1:1, v/v). The addition of acidified water greatly suppressed the formation of these adducts and aided protonation. The resultant mass spectrum recorded when 5 μg of the analyte in 1 μL was deposited on the paper substrate is shown in Figure 5.8. An intense, intact protonated molecular ion $[M+H]^+$ of metaldehyde at *m/z* 177, including a major fragment ion at *m/z* 149 were observed in the single stage MS analysis (Figure 5.8 a). This fragment ion (*m/z* 149) appears to be formed from the elimination of carbon monoxide (CO, *MW* 28 Da) gas, even prior to collisional activation suggesting a ring opening/rearrangement process in the presence of formic acid.

This observation was further investigated in two experiments: (i) studies of gas-phase fragmentation patterns in tandem MS experiments and (ii) detection of paraldehyde under acidified spray solvent conditions. First, the structure of the protonated metaldehyde, and its dissociation behaviour was characterized after collisional activation. Insert (i), Figure 5.8 (a) shows the product ion MS/MS mass spectra of the protonated metaldehyde. Unlike the sodiated molecular ion $[M+Na]^+$, which fragmented to give sodiated acetaldehyde, the protonated metaldehyde species dissociate predominantly via the loss of loss of CH_2=CH_2 to afford product ion at *m/z* 149. This fragmentation pathway indicates that the ion at *m/z* 149, observed in the full MS spectrum, is related to the metaldehyde protonated species, and confirms

the suggestion that the sodiated molecular ions are formed with minimal internal energy deposition. The second experiment to confirm the observed behaviour of the protonated metaldehyde involved the use of paraldehyde, a cyclic trimer of acetaldehyde molecules (metaldehyde being the corresponding tetramer). Figure 5.8 (b) shows the positive ion PS ionisation mass spectra of paraldehyde obtained when 5 μg of the sample in 1 μL was deposited on the paper substrate and sampled by using MeOH:(H_2O + 0.1% formic acid) as the spray solvent. A protonated molecular ion $[M+H]^+$ of paraldehyde at *m/z* 133 was observed. The structure of the protonated paraldehyde species was confirmed from CID fragmentation patterns as shown in insert (ii) (Figure 5.8 (b)) where the molecular ion yields an intense fragment ion at *m/z* 89 owing to the neutral loss of acetaldehyde (*MW* 44 Da). Like metaldehyde, the fragment ion at *m/z* 89 was observed in the single stage MS experiment.

The investigation of the structure/nature of the suspected ring "opened" product formed in the presence of formic acid was carried. As indicated above the elimination of 28 Da from metaldehyde was assigned to a loss of CH_2=CH_2 neutral species as illustrated in Scheme 5.2. This proposal is supported by the failure of acidified metaldehyde to react with hydroxylamine, both in solution and *in-situ* reactive paper spray experiments.

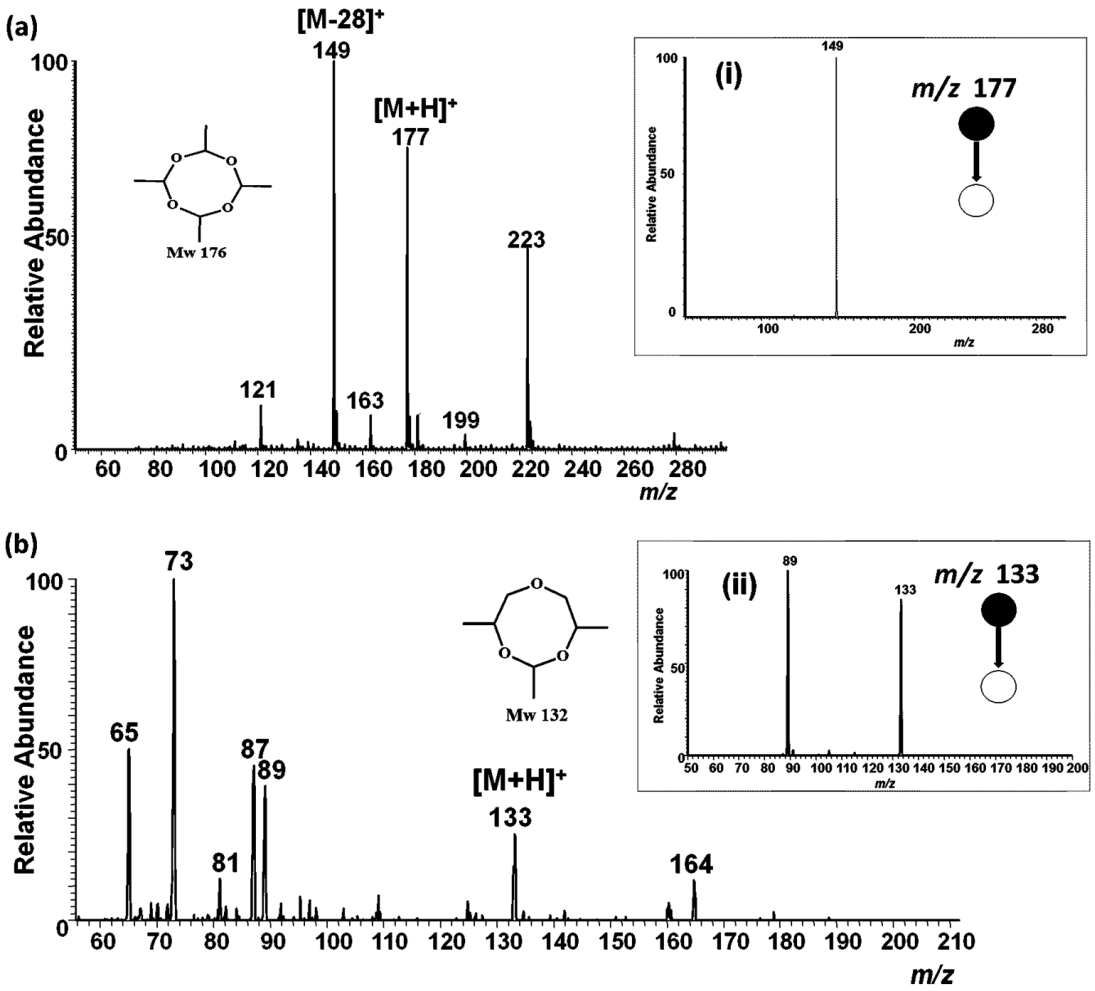
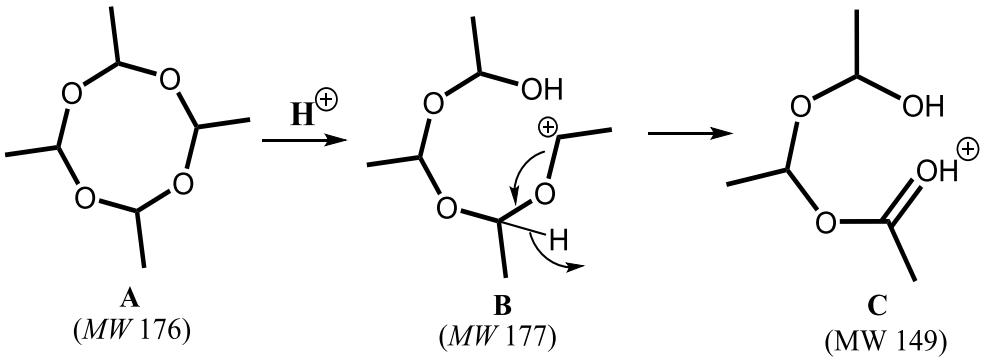


Figure 5.8**:** Positive ion mode paper spray mass spectrum using a bench-top ion trap mass spectrometer with MeOH:(H_2O + 0.1% formic acid) (1:1, v/v) spray solvent application. 5 µg of the analyte in 1 µL was spotted onto filter paper and ionised in air by application of a positive electric potential (3.5 kV); (a) metaldehyde and (b) paraldehyde. Insert (i) shows the tandem MS CID data for the *m/z* 177 ionic species and insert (ii) shows the tandem MS CID fragmentation distribution for the ion at *m/z* 177.

Product C is presumably formed via an internal proton hopping process and explains why both gas-phase CID and solution-phase rearrangements occur via a common ethylene loss. The ability to form a new ion type from metaldehyde simply by adding formic acid to the PS spray solution introduces an opportunity to differentiate metaldehyde from other potentially interfering ions having the same nominal mass. This advantage is particularly important for field metaldehyde

analysis in which the selectivity of the paper spray method can be increased by studying the fragmentation patterns of sodiated (formed using neutral spray solvent) and protonated (formed using acidified spray solvent) metaldehyde species.



Scheme 5.2: Proposed mechanism of acid catalysed for metaldehyde ring opening.

5.3.2.3 Direct PS-MS Quantification of Metaldehyde Ion Types PS

Fragmentation pathways for both the sodiated (*m/z* 199 → 67) and protonated (*m/z* 177 → 149) ion types were used to quantify metaldehyde in water. The limit of detection (LOD) was determined as the concentration that produces a signal more than three times greater than the standard deviation plus the mean value of the blank runs (in MS/MS mode). Using a commercial linear ion trap mass spectrometer, the detection limits for protonated and sodiated metaldehyde ions were determined to be ~0.05 ng/mL and 2.69 ng/mL, respectively using the PS ionisation method. Quantitative analysis of metaldehyde in water was achieved from the calibration curves shown in Figure 5.9, (3 ppb, *m/z* 221→179) as the internal standard, and monitoring analyte-to-internal standard ratios (A/IS) as a function of analyte concentration; this yielded good linearity (R^2 > 0.99) and precision (RSD < 10). We attribute the high sensitivity of the protonated ion type to the occurrence of only one

major fragment ion; that there are multiple and competing fragmentation pathways for the sodiated ion type depopulates the abundance of interested ions.

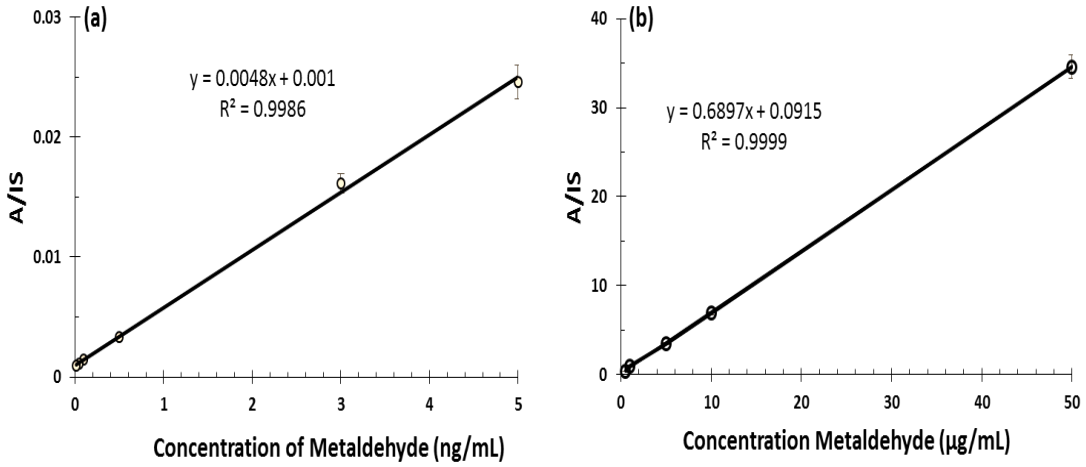


Figure 5.9 : **Calibration curve for quantification of metaldehyde in water using PS-MS/MS when analysing (a) protonated and (b) sodiated ion types produced in acidified and neutral spray solvents, respectively. Error bars indicate standard deviation from three replicates.**

As demonstrated, both qualitative and quantitative analysis of metaldehyde in water can be achieved using PS-MS with high sensitivity and selectivity. The LOD obtained suggests that PS-MS is suitable for the rapid detection of metaldehyde in water, although it registered higher values than those obtained from GC- and LC-MS analytical methods. With the ability of PS-MS to perform *in-situ* analysis on unmodified samples (see Table 5.1 for figures of merit), the methodology described in this study shows promise for use in routine investigative applications where regular monitoring or rapid screening is required.

Figure of Merit	PS-MS/MS
LOD^{x}: $[M+H]^+$ ion type	~0.05 ng/mL
LOD^{x}: $[M+Na]^+$ ion type	~2.69 ng/mL
Estimated sample prep. time	< ~60 seconds
In-situ analysis	Yes

X= Precision range ± 3.5 to 10 %

Table 5.1: Analytical performance of PS-MS/MS for analysis of metaldehyde in water.

5.3.2.4 Direct metaldehyde quantitation in environmental water samples

Direct analysis of metaldehyde in complex environmental water matrix using PS-MS was investigated without any sample preparation. A volume of ~10 μL from each sample was deposited onto the paper triangle and analysed using a commercial benchtop mass spectrometer in positive ion mode. Figure 5.10 shows the recorded mass spectrum for raw water samples (Chigwell Raw and Abberton Raw supplied by Northumbrian Water Ltd.) using either MeOH or MeOH:(H_2O + 0.1% formic acid) (1:1, v/v)) as the PS spray solvent. Intense protonated molecular ions of metaldehyde $[M + H]^+$ at *m/z* 177 were observed and confirmed by MS/MS CID experiments (insert (i) & (ii) in Figure 5.10) for the reactive experiment which utilised the acidic spray solvent.

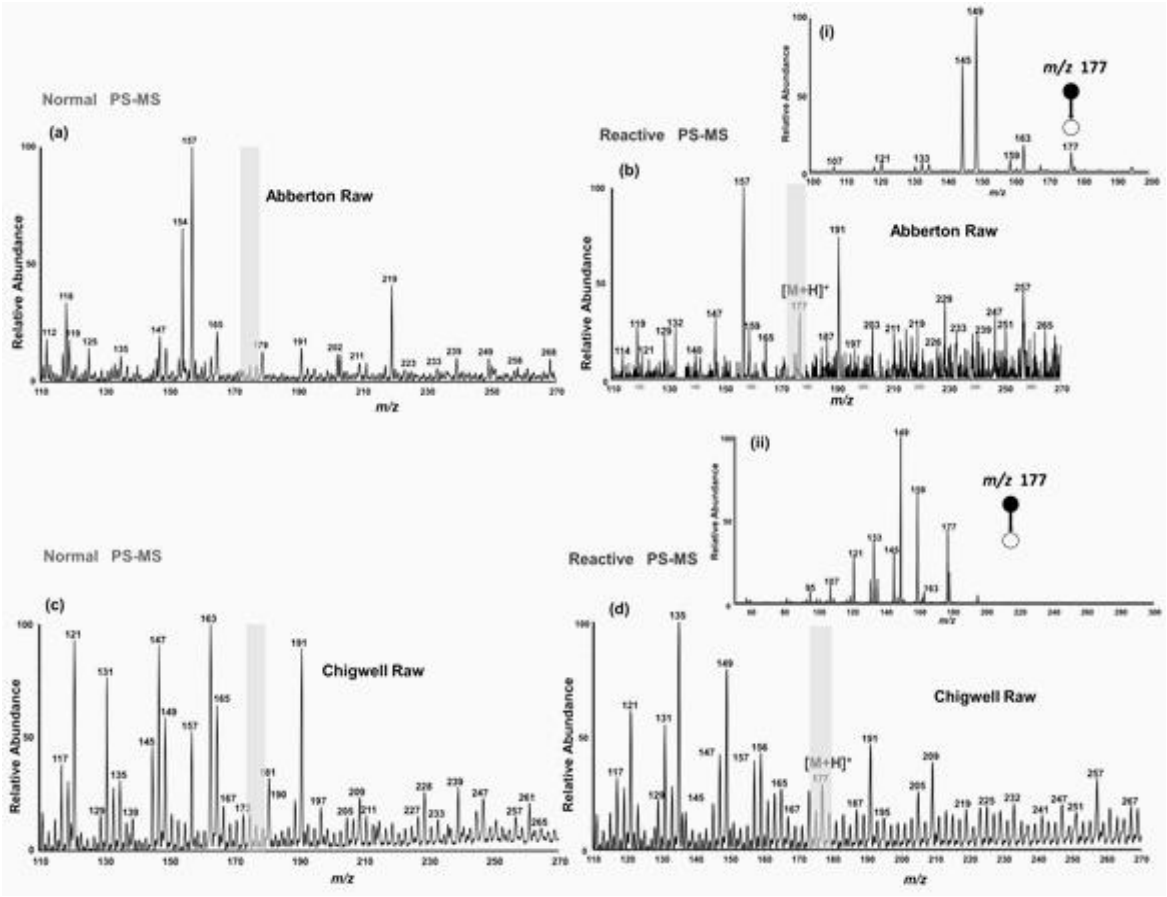


Figure 5.10: Positive ion mode paper spray mass spectrum for rapid detection of Metaldehyde in raw water samples (supplied by Northumbrian Water) whereby a volume of ~10 μL of the sample was deposited onto the paper surface and ionised in the open environment by application of an electric potential of +3.5 kV. Abberton Raw is analysed following the normal PS-MS method (a) and reactive PS-MS (b). Similarly for Chigwell Raw normal PS-MS (c) and reactive PS-MS (d) were utilised. Inserts (i) & (ii) are the MS/MS CID mass spectra for the protonated metaldehyde ion at *m/z* 177 from each water sample using the reactive methodology.

Rapid and direct analysis of metaldehyde has been described using paper spray mass spectrometry. Sodiated $[M+Na]^+$ and protonated $[M+H]^+$ molecular ions produced under two different spray conditions were characterized in which $[M+Na]^+$ species were identified to fragment through sequential loss of dimeric and monomeric acetaldehyde neutral species whereas $[M+H]^+$ dissociates via the elimination of ethylene. Quantitation of metaldehyde was achieved at low concentration (0.05 ng/mL for $[M+H]^+$ and 2.69 ng/mL for $[M+Na]^+$) in water using

the paper spray ionisation method. The MS/MS experiment provides a powerful means of qualitative analysis and definitive confirmation of metaldehyde in water.

The generation of different ion types in different spray conditions can offer an opportunity to readily discriminate (in the field) against other background ions with similar molecular weights since it is unlikely for a particular ion to fragment in a similar fashion as metaldehyde when using sodiated versus protonated parent ions in MS/MS. The demonstrated detection limit shows promise for the direct detection of metaldehyde in water at regulatory levels. Future work will involve development of a robust sampling procedure for onsite *in-situ* analysis of metaldehyde and related environmental contaminants using a portable mass spectrometer. This methodology can be extended to other pesticides that are of concern in the environment and the results are significant beyond the analysis of metaldehyde discussed herein as they represent a means for rapid analysis of environmental contaminants in water.

When combined with a miniature mass spectrometer, the simplicity of the PS-MS experiment itself makes for a potentially attractive on-site technique for water analysis and environmental monitoring. By using the leaf spray variant of the paper spray experiment [126, 127], this method can be readily adopted for the analysis and determination of metaldehyde on crops such as vegetables which may have been treated with the molluscicides [85, 128]. The ability to detect and characterize metaldehyde in raw water samples collected from natural water courses (supplied by Northumbrian Water Ltd, U.K.) has been demonstrated. In this experiment ~10 μL from each sample was deposited on the paper substrate and analyzed using PS-MS. Figure 5.10 shows the recorded mass spectra for Abberton Raw ((a) & (b)) and Chigwell Raw ((c) & (d)). Moderately intense protonated molecular ions $[M + H]^+$ of metaldehyde were observed for the reactive experiment

and confirmed using MS/MS CID data as shown in Figure 5.10, inserts (i) & (ii). The identification of the metaldehyde molecule in a variety of water samples demonstrates the utility of the PS-MS method for direct, rapid screening with little or no sample preparation.

5.3.3.0 *In-situ* Analysis of Corrosion Inhibitors in Petroleum Oil using PS-MS with a Portable Mass spectrometer

PS-MS method was utilised in the direct detection of quaternary ammonium salt corrosion inhibitors. The results obtained show that <0.1 ng/µL of quaternary ammonium salt in 1 µL oil (e.g., petroleum vacuum pump oil) placed onto paper can be detected with high sensitivity using either a commercial benchtop or a custom built miniature mass spectrometer Mini 12 [111]. This concentration (<100 ppb) of the active corrosion inhibitor is well below the reported minimum effective range of concentrations of these corrosion inhibitors, which is 50 – 200 ppm. The *In-situ* analyte(s) identification can be achieved by analysing the fragmentation patterns of the corrosion inhibitors generated using collision induced dissociation (CID) tandem mass spectrometry (MS/MS). This experiment worked well with both the commercial benchtop and the handheld mass spectrometer.

5.3.3.1 Quaternary Ammonium Corrosion Inhibitor Analysis using a Benchtop Ion Trap Mass Spectrometer

Two different groups of nitrogenous corrosion inhibitors (both quaternary ammonium salts) were studied by paper spray mass spectrometry. PS ionisation conditions (i.e. voltage, spray voltage) were first optimized using a benchtop ion trap mass spectrometer as described in [129] before mass spectra data for the quaternary ammonium corrosion inhibitor compounds was recorded. These

experiments were performed by applying: 0.1 ng/µL (1 µL of 100 ppb solution) of the corrosion inhibitor solution in vacuum pump oil, to a paper triangle, then adding acetonitrile/methanol solvent (1:1 v/v), and recording data using the Thermo LTQ. These mass spectra recorded showed intact cations with little or no fragmentation or interference from the oil matrix (Figure 5.11). The remarkable absence of signal due to the oil components is consistent with the high ionisation efficiency of pre-charged organic salts, a well-known feature of many different types of ionisation methods.

Characterization of the individual intact cations was achieved by tandem mass spectrometry; for example, insert (ii) of Figure 5.11 (a) shows that CID of the intact tetraoctylammonium cation at *m/z* 466.6 gives two fragment ions (a major and minor) at *m/z* 354.5 and 352.5 respectively with a loss of neutral octene (MW 112) and octane (MW 114) respectively [110]. The stability and abundance of the product ion allowed three-stage mass spectrometry (MS/MS/MS) experiments to be performed. In this particular case, CID of the product ion at *m/z* 345.5 yielded further fragment ions at *m/z* 242 (major) and *m/z* 240 (minor) through sequential losses of octene (presumably 1-octene, CH_3-$(CH_2)_5$-CH=CH_2, MW 112) and octane (presumably n-octane, CH_3-$(CH_2)_5$-CH-CH_2, MW 114). Such multiple-stage MS experiments allow definitive confirmation of the identity of the analyte(s) [110].

Similarly, other model compounds including hexadecyltrimethylammonium bromide, tetradodecylammonium bromide, tetrahexylammonium bromide, and benzylhexadecyldimethylammonium chloride were analysed by PS-MS using the Thermo LTQ commercial instrument (see Appendix E.2 to E.5 for more details). The nitrogenous corrosion inhibitors are available with different counter ions, a property that influences the inhibition performance of the salts [130]. As demonstrated by the analysis of tetrabutylammonium hexafluorophosphate (Figure 5.11 b), positive ion

PS-MS method is insensitive to the type of anion associated with the quaternary ammonium cation. It was also found that both short and long chain cations can be analysed effectively. Table 5.2 provides a summary of data for all the model compounds studied, including their CID fragmentation patterns. Just as in the case of the tetraoctylammonium cation (Figure 5.11 (a), the elimination of a neutral alkene (C_nH_{2n}) and alkane (C_nH_{2n+2}) was observed during CID for all alkyl quaternary ammonium cations studied (Scheme 5.3 (a) and (b). It is important to note that the fragmentation pattern was also observed for the long and short chain quaternary ammonium corrosion inhibitor model compounds. For example, MS^2 and MS^3 spectra for the short chain tetrabutylammonium cations at *m/z* 242 and *m/z* 186 via successive eliminations of butene (MW 56) and butane (MW 58) are evident in Figure 5.11 (b) insert (v) and (vi).

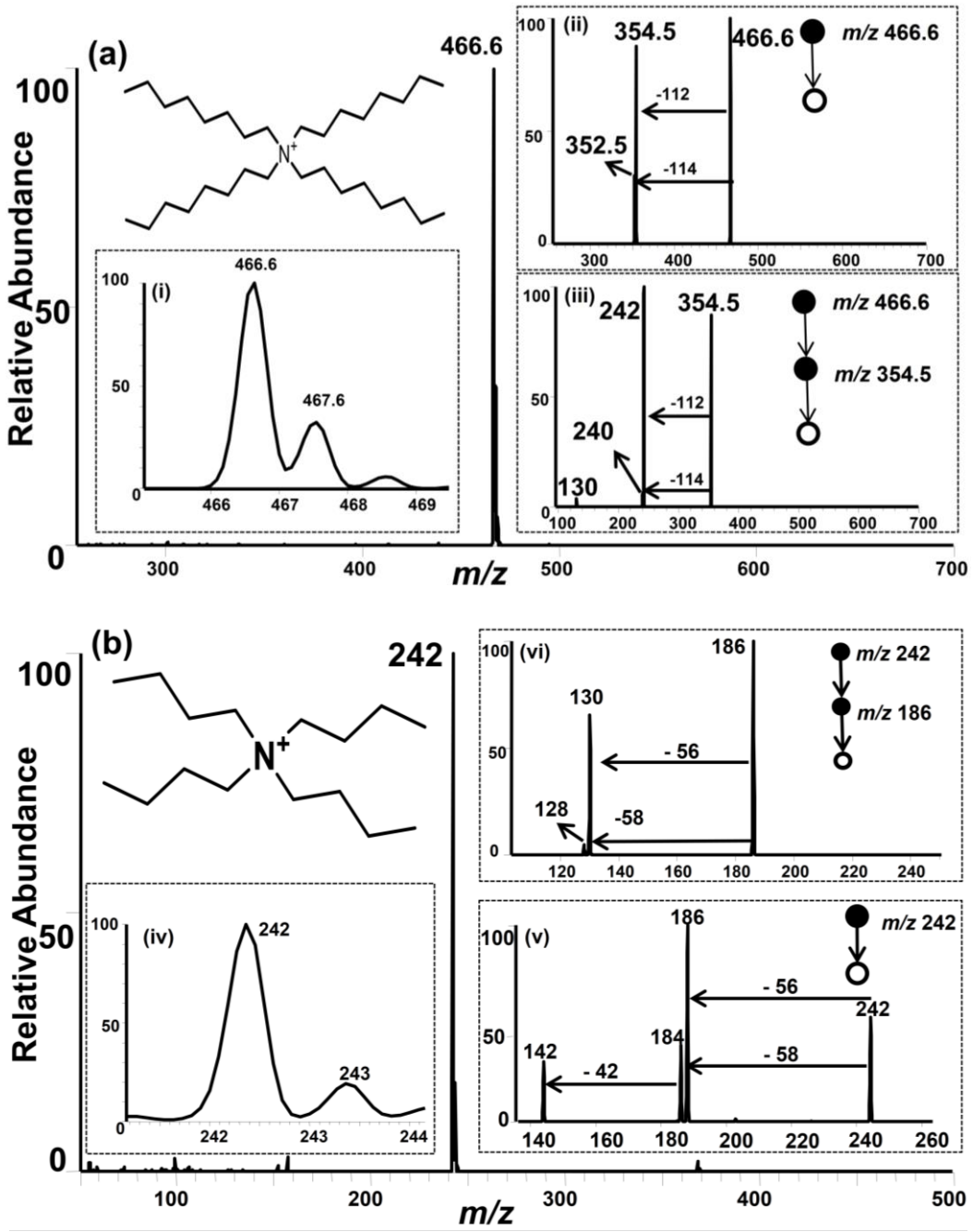


Figure 5.11: Positive ion mode paper spray mass spectrum for quaternary ammonium corrosion inhibitor model compounds analysed using a benchtop ion trap instrument. Absolute amounts of analyte(s) spotted onto filter paper and ionised in air by application of an electric potential were 100 pg of each compound in 1uL of oil, viz.100 ppb (a) tetraoctyl ammonium bromide at *m/z* 466.6, (b) tetrabutylammonium hexafluorophosphate at *m/z* 242. Insert (i) shows the isotopic distribution of the isotopic distribution of the analyte ion and inserts (ii)-(vi) show MS/MS CID data for selected ions, again using 100 pg of analyte in 1µL of oil.

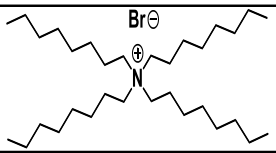
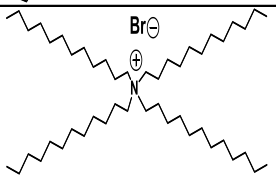
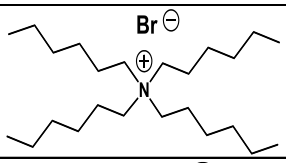
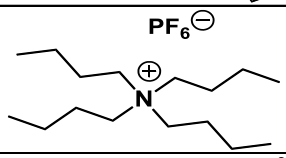
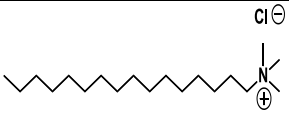
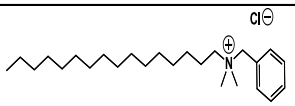
Name	Structure	MW (cation)	MS^2 Transitions	MS^3 Transitions
Tetraoctylammonium bromide		466.6	466.6→354.5 (loss of C_8H_{16}) 466.6→352.5 (loss of C_8H_{18})	466.6→354.5→242 (Loss of C_8H_{16}) 466.6→352.5→240 (Loss of C_8H_{18})
Tetradodecylammonium bromide		691.0	691→522 (Loss of $C_{12}H_{24}$) 691→520 (Loss of $C_{12}H_{26}$)	691→522→354.5 (Loss of $C_{12}H_{24}$) 691→520→352.5 (Loss of $C_{12}H_{26}$)
Tetrahexylammonium bromide		354.7	354.7→270 (loss of C_6H_{12}) 354.7→268 (loss of C_6H_{14})	354.7→270→186 (C_6H_{12}) 354.7→268→184 (C_6H_{14})
Tetrabutylamonium hexafluorophosphate		242.0	242→186 (loss of C_4H_8) 242→184 (loss of C_4H_{10})	242→186→130 (loss of C_4H_8) 242→186→128 (loss of C_4H_{10})
Hexadecyltrimethylammonium bromide		284.0	Below Scan range	Below scan range
Benzylhexadecyl dimethylammonium chloride		360.0	360→168 (loss of C_7H_8)	Below scan range

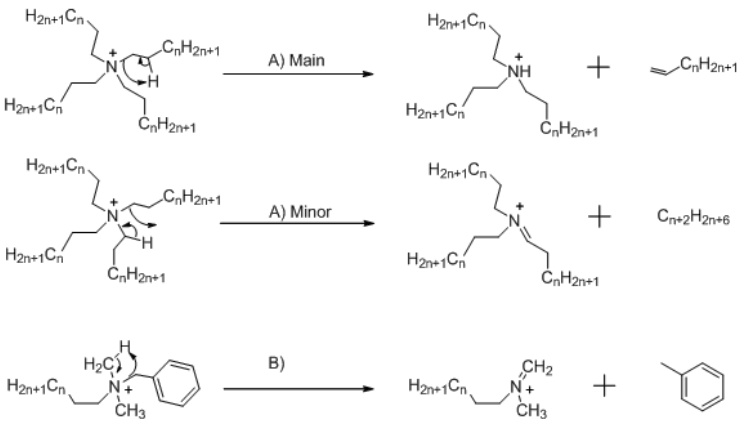
Table 5.2: Structures and CID product ions of quaternary ammonium compounds analysed in oil.

5.3.3.2 Complex Mixture Analysis Using Paper Spray Ionisation

Ionisation using PS-MS was also used to analyse quaternary ammonium corrosion inhibitors in mixtures. Firstly, an artificial mixture was prepared using equal volumes of the quaternary ammonium corrosion compounds in acetonitrile/methanol (1:1, v/v) to form a mixture of active corrosion inhibitor components. The mixture was then analysed by PS-MS under the same conditions as described above: i.e., 10 pg of each compound (in 1µL of oil) of corrosion inhibitor solution was spiked onto a paper triangle and analysed using the commercial ion trap mass spectrometer, (as shown in Appendix E.1) with a typical mass spectrum being

shown in Appendix E.6. Next a second mixture including alkyldimethylbenzyl ammonium chloride salts was prepared by mixing equal amounts of the model compounds in pump oil. Analysis of this mixture by PS-MS was again achieved without any sample pre-treatment, and the resulting mass spectrum is shown in Figure 5.12. Both mixtures gave relatively stable PS signals and produced no observable ion fragmentation in the full scan mass spectrum.

Relative signal intensities from these corrosion inhibitor mixtures in pump oil corresponded to the amounts in the analyte mixture. Changing the spray solvent from methanol to methanol/acetonitrile showed no effect on the ion signal intensity of signal to noise ratio as described in Appendix E.7. Note that this standard sample (alkyldimethylbenzyl ammonium chloride) contains only trace amounts of C_{16} and this is evident from the relative abundance of this mass spectral signal from this ion compared with that of other components in the mixture Appendix E.7 and in the corresponding total ion chronograms (TIC). In the latter experiment, no *m/z* 360 (C_{16}) ion signal is observed at 5.5 min, for details see Appendix E.8.



Scheme 5.3: Suggested fragmentation pathway for the A) alkyl and B) benzyl-substituted ammonium salts model compounds based on MS/MS CID data.

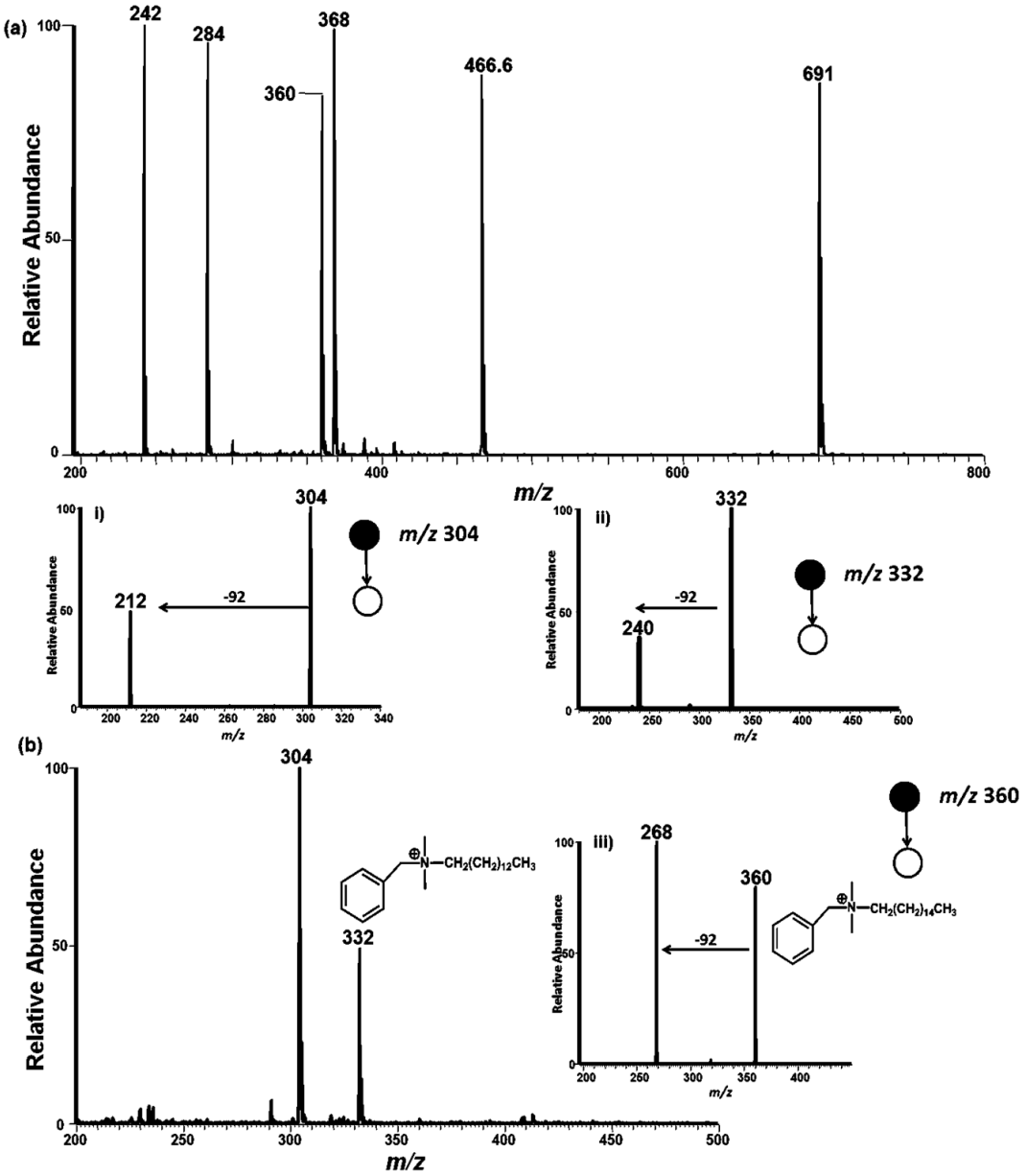


Figure 5.12**:** (a) Positive ion mode paper spray mass spectrum for the model compounds in mixtures in vacuum pump oil analysed using a benchtop instrument; tetrabutylammonium bromide gives the intact cation at *m/z* 242, hexadecytrimethylammonium bromide at *m/z* 284, benzylhexadecyldimethylammonium chloride at *m/z* 360, tetraoctylammonium bromide at *m/z* 466.6 and tetradodecylammonium bromide at *m/z* 691. (b) Typical positive ion paper spray mass spectra for alkyldimethylbenzyl ammonium chloride $[C_6H_5CH_2N\ (CH_3)_2R]Cl$ where R is predominantly n-$C_{12}H_{25}$ but also contains C_{14} and C_{16} homologs) standard analysed using a benchtop ion trap mass spectrometer. Insert i), ii) and iii) are the MS/MS CID mass spectra for the *m/z* 304 (C_{12}), *m/z* 332 (C_{14}), *m/z* 360 (C_{16}) respectively.

5.3.3.3 *In-situ* Analysis of the Ammonium Quaternary Corrosion Inhibitor in Petroleum Oil using PS with A Miniature Mass Spectrometer (Mini 12)

The success of PS-MS in the analysis of quaternary ammonium salts from an oil matrix using the benchtop instrument was encouraged us to transfer this experiment to a miniature ion trap instrument (Mini 12.0). Mixtures as well the individual alkyl and benzyl quaternary ammonium corrosion inhibitor formulations were analyzed using the Mini 12.0 with paper spray ionisation. Figures 5.13, (a) and (b), show the data for 1ng/µL for tetraoctylammonium bromide and benzylhexadecyldimethylammonium chloride, applied to the paper substrate in 1 µL of petroleum pump oil. As can be observed, PS-MS using the Mini 12.0 gives a high ion signal-to-noise ratio even at this low level of analyte(s). Both the LTQ and the Mini 12 instruments signals are high enough to allow the identity of these compounds to be easily confirmed by tandem MS.

Compound	LOD using commercial ion trap (pg) [xx]		LOD using mini ion trap (pg) [yy]	
	neat solvent	**Oil matrix**	**neat solvent**	**Oil matrix**
Tetraoctylammonium bromide	0.9	1.1	81	184
Tetrahexylammonium bromide	0.6	9.5	*n.a.*	*n.a.*
Tetrabutylamonium hexafluorophosphate	0.9	11.6	*n.a.*	*n.a.*
Benzylhexadecyldimethyl ammonium chloride	10.2	27.6	282	472

n.a = not available

xx = Precision range ± 2.5 to 12 %

yy = Precision range ± 6.5 to 15 %

Table 5.3: Detection limits (LOD) of the analysed quaternary ammonium model compounds in pg absolute.

Even though the Mini 12.0 mass spectrometer operates at a relatively high pressure compared with the commercial instrument, little fragmentation was observed in the full scan mass spectra. The structural information however, is readily available from MS/MS (Figures 5.14 (c) and (d). Again, the tetraoctyl ammonium cation, *m/z* 466, fragments on the Mini 12.0 instrument through sequential loss of octene (MW 112) to give ions at *m/z* 354, 244 and 130. By contrast with the alkyl ammonium salts, the most stable neutral species eliminated from the intact cation, *m/z* 360, of the alkyl quaternary ammonium salt, benzylhexadecyldimethyl ammonium during CID is toluene (MW 92) and not an alkene derived from the alkyl groups attached to the quaternary nitrogen (Scheme 5.2 (c). This fragmentation pathway yields a product ion at *m/z* 268 (Figure 5.14 (d). Such a simple fragmentation allowed easy quantification of various quaternary ammonium alkyl salts having different alkyl chain lengths in petroleum vacuum pump oil (Table 5. 4).

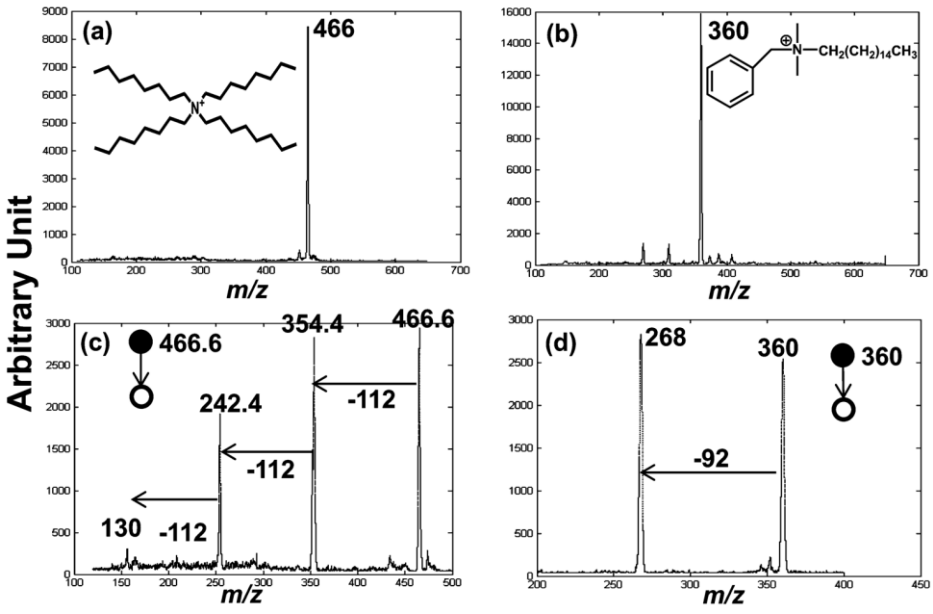


Figure 5.13**:** Positive ion paper spray mass spectra of quaternary ammonium corrosion inhibitor model compounds analysed in oil (1 μL) using a handheld miniature instrument. Absolute amounts of analytes spotted on paper were 100 pg of each compound. (a) tetraoctyl ammonium bromide, (b) benzylhexadecyldimethyl

ammonium chloride in vacuum pump oil artificial mixture, (c) and (d) are the CID mass spectra of the samples respectively.

Active corrosion compound	**MW (Cation)**	**MS/MS Transitions**	**Ion Loss**
Quat C_{12}	304	*m/z* 304 → 212	92
Quat C_{14}	332	*m/z* 332 → 240	92
Quat C_{16}	360	*m/z* 360 → 268	92

Table 5.4: Structures and product ions of CID of $[C_6H_5CH_2N\ (CH_3)_2R]Cl$ analysed in Pump Oil by PS-MS on benchtop and miniature Instruments.

The paper spray ambient ionisation/Mini 12.0 combination was also used for mixture analysis. To test this capability, a standard mixture of alkyl dimethyl benzyl ammonium chloride [i.e., a salt having n-alkyl substituents C_{12} (major), C_{14} and C_{16}] obtained from Sigma Aldrich (St. Louis, MO) was dissolved in petroleum vacuum pump oil. A second mixture consisting of five corrosion inhibitors dissolved in methanol/acetonitrile (1:1, v/v) was prepared in house by mixing equal amounts of tetrabutyl ammonium bromide, hexadecyltrimethyl ammonium bromide, benzylhexadecyldimethyl ammonium chloride, tetraoctyl ammonium bromide and tetradodecylammonium bromide in petroleum vacuum pump oil. Typical mass spectra obtained for the two different mixtures using the Mini 12.0 are shown in Figures 5.14 (a) and (b), when 100 pg/µL was examined on paper using the Mini 12.0 instrument. For the artificial quaternary ammonium salt mixture, the components in the mixture were observed at *m/z* 242, 284, 354, 360 and 466. For the standard mixture of alkyl quaternary ammonium salts, only two out of the three mixture components (i.e., C_{12} and C_{14}) were typically observed in the full scan mode

using either the benchtop commercial or the Mini 12.0 instruments (Figure 5.14 (b) when 1 ng/µL of the mixture was spiked onto the paper. This is simply because the amount of *m/z* 360 (C_{16}) benzylhexadecyldimethyl ammonium chloride salt in the mixture was smaller than that of *m/z* 332 (C_{14}), which was in turn smaller than *m/z* 304 (C_{12}). The *m/z* 360 (C_{16}) component could, however, be identified and confirmed at *m/z* 360 using the MS/MS experiment as shown in insert iii) Figure 5.13, insert iii) and Figure 5.14 (d). Structural information was obtained for each member of the two mixtures, examples of which are provided in Figures 5.15 (c) and (d) using the Mini 12.0 handheld miniature mass spectrometer.

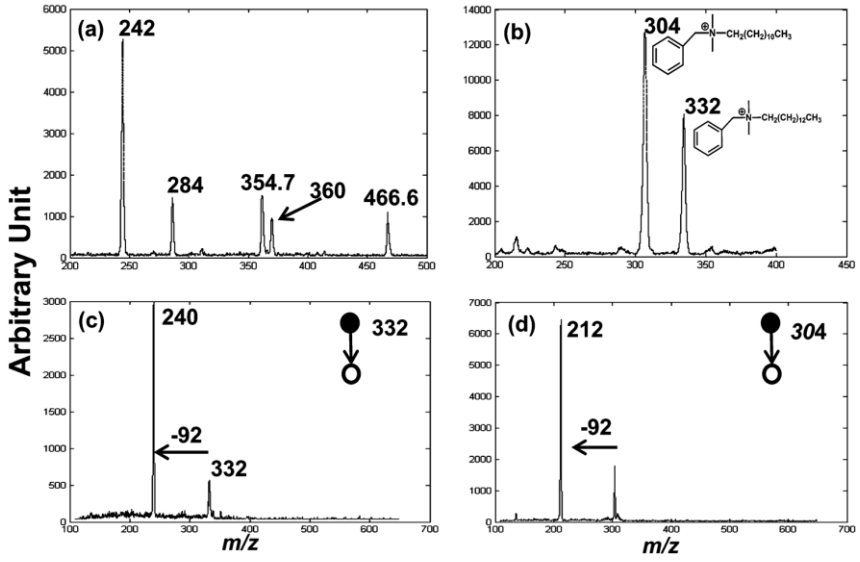


Figure 5.14**:** (a) Positive ion paper spray mass spectrum for the model compounds artificial mixtures in vacuum pump oil analysed using a handheld miniature instrument absolute amounts of analytes spotted on paper were 1 ng/µL (absolute concentration); tetrabutyl ammonium bromide at *m/z* 242, hexadecytrimethyl ammonium bromide at *m/z* 284, benzylhexadecyldimethyl ammonium chloride at *m/z* 360, tetraoctyl ammonium bromide at *m/z* 466.6 and tetradodecylammonium bromide at *m/z* 691, (b) Typical positive ion paper spray mass spectra for alkyldimethylbenzyl ammonium chloride $[C_6H_5CH_2N\ (CH_3)_2R]Cl$ where R is predominantly n-$C_{12}H_{25}$ but also contains *m/z* 332 (C_{14}) and *m/z* 360 (C_{16} homologs) standard analysed using a benchtop ion trap mass spectrometer, (c) and (d) show the CID MS/MS data for the of *m/z* 304 (C_{12}) and *m/z* 332 (C_{14}) mixture components, respectively.

5.5.0 Conclusions

Direct analysis of long chain aliphatic primary polydiamines by PS-MS has been demonstrated in a variety of boiler water samples with little or no sample pre-treatment in open air. The use of tandem mass spectrometry analysis assisted in confirming the identity of aliphatic primary amine (Duomeen® O) in various boiler system water samples. Exact mass measurements using and LTQ-Orbitrap further confirmed that the Duomeen® O molecule formula was observed within 1 ppm mass accuracy. PS-MS ambient ionisation is both sensitive and selective for the analysis of corrosion inhibitor formulations in boiler water samples. Linear signal responses with a dynamic range of 5 orders of magnitude were obtained. The LOD of 0.1 pg (absolute concentration) with reproducibility of RSD of < 10 % is noteworthy for the direct analysis of corrosion inhibitor formulations (i.e. aliphatic primary polydiamine and amine) in crude large medium pressure (MP) water tube boiler plant samples.

Furthermore, the Schiff-base reaction between the aliphatic primary polydiamine (Duomeen® O) and acetone complements the usefulness of PS-MS analyte molecules in complex sample mixtures. The simplicity of paper spray ionisation and the ability to analyse raw boiler water samples without sample preparation further enhances the potential for coupling to a portable or miniaturized mass spectrometer for onsite analysis. Such a system in operation would be of great value in the water industry for quality control. Future work will consider PS ionisation coupled to portable miniature mass spectrometers for in-field characterization of different boiler water samples under ambient conditions. Online *in-situ* with online monitoring of the water boiler system is the ultimate aim**.**

Rapid and direct analysis of metaldehyde has been described using paper spray mass spectrometry. Sodiated $[M+Na]^+$ and protonated $[M+H]^+$ molecular ions produced under two different spray conditions were characterized in which $[M+Na]^+$ species were identified to fragment through sequential loss of dimeric and monomeric acetaldehyde neutral species whereas $[M+H]^+$ dissociates via the elimination of ethylene. Quantitation of metaldehyde was achieved at low concentration (0.05 ng/mL for $[M+H]^+$ and 2.69 ng/mL for $[M+Na]^+$) in water using the paper spray ionisation method. The MS/MS experiment provides a powerful means of qualitative analysis and definitive confirmation of metaldehyde in water.

The generation of different ion types in different spray conditions can offer an opportunity to readily discriminate (in the field) against other background ions with similar molecular weights since it is unlikely for a particular ion to fragment in a similar fashion as metaldehyde when using sodiated versus protonated parent ions in MS/MS. The demonstrated detection limit shows promise for the direct detection of metaldehyde in water at regulatory levels. Future work will involve development of a robust sampling procedure for onsite *in-situ* analysis of metaldehyde and related environmental contaminants using a portable mass spectrometer. This methodology can be extended to other pesticides that are of concern in the environment and the results are significant beyond the analysis of metaldehyde discussed herein as they represent a means for rapid analysis of environmental contaminants in water.

When combined with a miniature mass spectrometer, the simplicity of the PS-MS experiment itself makes for a potentially attractive on-site technique for water analysis and environmental monitoring. By using the leaf spray variant of the paper spray experiment [126, 127], this method can be readily adopted for the

analysis and determination of metaldehyde on crops such as vegetables which may have been treated with the molluscicides [85, 128].

Direct analysis of corrosion inhibitor active components at very low concentrations (< 1 ng/μL) in complex oil mixtures has been demonstrated using paper spray ionisation using a portable handheld mass spectrometer. The MS/MS experiment provides a powerful means of qualitative analysis. The resolution of the miniature ion trap instrument is adequate for these experiments (unit resolution over the mass range of interest) and the detection limit is only a factor of ca. 10 more than in the commercial benchtop instrument. This detection limit is adequate for the direct detection of corrosion inhibitor concentration levels. Hence the results shown are promising for the analysis of corrosion inhibitor concentrations at levels appropriate to manage the treatment of transmission pipelines. Future work will involve on-site analysis of the corrosion residuals in real samples. The capabilities of this methodology will be extended to other oilfield chemicals that are also important such as scale inhibitors. The results are significant beyond the petroleum problem discussed because they represent a rigorous test of miniature mass spectrometer performance in trace analysis of complex samples.

The reported study encourages the future development of disposable 3D microfluidic paper-based analytical devices, which function with simple operation but capable of on-chip analyte(s) detection by MS; such a device can replace the traditional complex laboratory procedures for MS analysis to enable on-site *in-situ* sampling with portable mass spectrometers.

5.5.0 References

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Chapter 6: Concluding Remarks and Future Perspectives

6.1 Concluding Remarks

Ambient ionization mass spectrometry (AI-MS) has become an indispensable versatile analytical tool for the identification and quantification of a wide range of unmodified chemicals, primarily because of its speed, sensitivity and specificity, especially when tandem MS (MS/MS) is performed [1-9]. AI-MS offers to the analyst: simple, robust, and fast tools for direct analysis of a wide range of samples [10]. AI-MS has impacted many areas of science ranging from; physics for material synthesis using ambient soft-landing [11-13], chemistry for chemical identification, structure elucidation and quantification, in life sciences for disease diagnosis and drug development [14]. Using a combination of a mass spectrometer instrument and a single or a combination of desorption/ionisation ambient ionisation (AI) sources [15], AI-MS can be used as a universal, 'soft' or non-destructive analytical tool, amenable to almost all biological, environmental and forensic samples. Reduction in the sample preparation time, which is an obligatory in traditional MS, is no longer required in AI-MS. This is an enormous breakthrough, finally removing/reducing labour intensive sample preparation procedures for MS in the field of analytical science. In the last five years more than five AI-MS instruments have been commercialized and approximately ten laboratory/research based AI sources are introduced to the scientific community every year [16].

Miniature and portable mass spectrometers are becoming commercially available [17-19]. Portable light-weight vacuum pumps weighing less than 5 kg have become commercially available [20] and the long-awaited prospect of handheld AI-

MS analysis is now possible. The deployment of a portable or miniature MS systems combined with ambient desorption/ ionisation techniques will simplify real time on-site *in-situ* applications, for example, in manufacturing, in hospitals for point–of–care diagnosis, at the water treatment facilities, on the battlefield, at the sports ground and for crime scene investigations. On-site pre-selection of evidence by AI-MS would be of a great benefit for the sporting authorities (FIFA and WADA), for homeland security and boarder agencies, lowering the burden on national analytical laboratories. Further developments are needed in terms of new applications as well as improvements in the ionisation methods and mass spectrometer instrument miniaturization and portability.

In this regard, herein new analytical methodologies that will advance the application of AI-MS for *in-situ* have been developed and demonstrated for the direct analysis and quantification of: petroleum fuels, water and petroleum oil additives (i.e. corrosion inhibitors), polycyclic hydrocarbons (PAHs) and molluscicide (Metaldehyde) *in-situ* with little or no sample preparation. The analytical methods developed are based on desorption atmospheric pressure chemical ionisation (DAPCI) and paper spray (PS) AI-MS. The results reported demonstrate the utility of AI-MS with MS/MS for *in-situ* analysis, quantification of a wide range of analyte(s) in complex sample matrixes (i.e. water and petroleum oil) with high sensitivity and selectivity as summarized below:

1) **Observation of molecular Ions and protonated molecules in desorption atmospheric pressure chemical ionisation (DAPCI) (Chapter 2):**

This chapter describes the ionisation mechanism of DAPCI and its application to the *in-situ* analysis of different hydrocarbon systems under ambient conditions with little or no sample preparation. In DAPCI ionisation conditions were chosen to determine

whether protonated molecules are generated via proton transfer, or molecular ions are generated via electron transfer. The protonated molecule $[M+H]^+$ and the hydride abstracted $[M-H]^+$ form were observed when using an inert gas, typically nitrogen, to direct a lightly ionised plasma generated by corona discharge onto the sample surface in air. In contrast, the introduction of a head space vapour of naphthalene into the DAPCI gas stream yielded a molecular radical cations ($M^{+\bullet}$); in this case the ionised radical cation (at *m/z* 128) served as a charge exchange reagent for model hydrocarbon compounds that are difficult to ionise using normal DAPCI ionisation mode. This mode of sample ionisation provided mass spectra with better signal/noise ratios and without unwanted side-products (e.g. oxidation, etc.). The thermochemistry governing the individual ionisation processes is discussed, and a desorption/ionisation mechanism is inferred [21-24].

2. On-site chemical analysis Using DAPCI ion source coupled to a portable mass spectrometer (Chapter 3):

This chapter demonstrates the coupling of the DAPCI ion source with a portable mass spectrometer for "near-instant", *in-situ* detection of polar alkylated benzenes and non-polar PAHs that are difficult to analyze. The results obtained indicate that these PAHs can be detected from ambient surfaces instantly with little or no sample preparation. Structural characterization and the identities of these PAHs were confirmed using tandem mass spectrometry (MS/MS) [25].

3. A handheld portable DAPCI ion source for on-site point and shoot applications (Chapter 4):

This chapter presents the design and operation of a novel, cylinder-and-solvent free, light-weight handheld ion source based on the use of a DAPCI source weighing <0.6 kg. The source was used for the analysis of nitroaromatic explosives on surfaces in

open air, demonstrating portability for in-field applications. The advantages of low carrier gas, and low power consumption (< 6 W), as well as zero solvent usage allow trigger-based, “near real-time” sampling/ionisation was demonstrated. The ability to perform direct detection of several nitroaromatic explosive compounds in a complex mixture without prior sample preparation is also demonstrated and the identities of each individual explosive in the mixture were confirmed by M/MS CID fragmentation patterns [26-29].

4. *In-situ* Analysis of Water and Petroleum Oil Samples Using Paper Spray Ionisation (Chapter 5):

In this chapter *in-situ* the analysis and identification of long chain aliphatic primary (polyamines) and quaternary ammonium corrosion inhibitors in water and petroleum samples is demonstrated for the first time, without any sample preparation using paper spray mass spectrometry (PS-MS). The minimum level of the individual corrosion inhibitors that could be detected in both water and petroleum oil samples using PS-MS was <0.1 pg (absolute concentration). PS-MS was also applied to the direct detection of metaldehyde in water samples. Using a commercial linear ion trap mass spectrometer, in the MS/MS mode metaldehyde residues were detected in water samples at low concentration (LOD ~ 0.05 pg/mL) without any pre-concentration/separation steps.

In summary, *in-situ* MS analysis under atmospheric pressure is demonstrated in which analyte(s) can be analysed in the open air in their native environment with little or no sample preparation. Also a method for *in-situ* chemical derivation of primary amine corrosion inhibitor formulations in water samples using paper spray mass spectrometry at atmospheric pressure has been developed, and the fundamentals of *in-situ* ion generation and ion-molecule reactions under atmospheric conditions are demonstrated.

6.2 Future Perspectives

A century has passed since the fundamental work of Thomson, who is widely regarded as the pioneer of MS [9]. Thomson realized the enormous potential of the technique. This was exemplified by his writing in 1913 [30], *"there are many problems in Chemistry which could be solved with far greater ease by this [method]."* Judging by the scope and extensive use of MS in the present day, Thomson may have understated the potential. MS is today an established *bona fide* clinical tool, a ubiquitous and indispensable research instrument with an extremely wide range of applications. Arguably, no other device has contributed to so many fields over the past 100 years.

The path ahead for MS seems certain to include much more emphasis on multiplexed (orthogonal) measurements and instrumentation, especially in the realm of MS imaging. Multidimensional imaging, e.g., MS with X-Ray computerized tomography (CT) and Magnetic Resonance Imaging (MRI), is currently an active area of research [31, 32]. Further developments in MS-based proteomics as a tool for new drug discovery and/or biomarker determination could lead to personalized drug development to inactivate specific proteins linked with particular disease conditions [33]. Due to the increasing rate and amount of data acquisition in MS, developments in the handling and processing of 'big data' [34, 35] will play a key role in the future of MS.

The need to analyse many more samples from biomedical, clinical, sports industry, environmental and public safety areas will require higher throughput, onsite (point-of-use) measurements and smaller, more specialized instrumentation. The capabilities of ambient ionisation methods are particularly well suited to these high

volume applications in that sample preparation is minimized/removed [2]. Advances in MS miniaturization, portability, versatility and ruggedness will lead to mass spectrometers being deployed in a variety of harsh environments [36] not limited to our own planet [37, 38]. The presence of toxic and potentially hazardous compounds in our environment, forensic settings, and the increasing need to monitor biological compounds produced in *vivo,* demands the development of on-site analytical systems with the ability to detect a wide range of analyte (s) *in-situ* with little or no sample preparation. Despite the extensive use of MS, it is not an ideal method for all analyses; sample preparation before introduction into a mass spectrometer can be laborious and time-consuming, and many applications are limited by the inconvenience of *ex-situ* MS analysis. Furthermore, samples are always transported to centralised laboratory for analysis.

MS analysis under atmospheric pressure is demonstrated in which Analyte(s) can be analysed *in-situ* in their native environment with little or no sample preparation under atmospheric pressure conditions. A method for *in-situ* chemical derivation of primary amine corrosion inhibitor formulations in water samples using paper spray mass spectrometry at atmospheric pressure has been developed. Fundamental of *in-situ* ion generation and ion-molecule reactions under atmospheric conditions, has been demonstrated.

The current work focused on researching *in-situ* MS as an analytical instrument for generating intact molecular ions, focusing and using them as ordinary reagents for organic reactions at ambient surface in open air, outside the mass spectrometer. Most of my future projects will build on this innovation, but instead of simple organic compounds, I will focus on biomolecules of specific biological importance. As such, the overall objective of my future research will involve

extending the developed ambient ionization methods (i.e. DAPCI and PS) from simple environmental organic compounds to biological molecules. For example, a major effort will be dedicated to the introduction of charged aerosols for treating respiratory diseases. This work can involve investigating the possibility of using molecular ions generated using ambient ionization sources in medicine for disease treatment. This can be achieved due to the fact that ions are more reactive than their neutral counterparts, especially when confined, and might exhibit a much faster immune response. For certain medical conditions (e.g., treatment of acute symptoms including asthma, migraine, panic disorder, etc.), fast drug delivery and response is critical. Intravenous infusion is the fastest means to deliver drugs, but it is impractical for outpatients. One promising route involves inhalation of aerosols directly into the lungs, since the alveolar blood supply passes directly to the pulmonary vein, left heart and arterial circulation. Interestingly, there are analogous methods in mass spectrometry for generating intact molecular ions. Although not reported, one can hypothesize that some of the aerosol generators may produce charged particles. My approach to investigating this hypothesis is to select an aerosol generator (e.g., ultrasonic nebulizer) and use it, with some modifications; as an ion source in MS. Ion currents will be measured outside the MS instrument, and the nature of ions will be characterized via mass analysis and tandem MS.

This basic new idea of aerosol mass spectrometry will opens doors to several exciting new areas in life sciences. Examples include aerosol therapy (i.e. charged vs. neutral particle) and the investigation of the presence and nature of charged particles in various aerosols used to treat lung diseases and microbial detection and control for rapid and efficient surface disinfection by delivering the disinfectants (e.g., aldehydes) in the form of charged aerosols. Specifically, this work will focus

on the establishment of analytical protocols that allow on-surface splitting of solvents, for multiplexed detection, rapid immuno-extraction and concentration of the analyte(s), and ambient paper spray (PS) ionisation mass spectrometry (MS), all from a single paper device such as the handheld DAPCI developed in this thesis.

The need for on-site, instant analysis of suspected toxic and hazardous compounds in our environment is thus a clear and present need for the first responders in the homeland security, defence, forensics, and environmental contexts. It is difficult to forecast with confidence what developments will be made in the field of MS and where future advances will take us; however, extrapolating from the immediate past, the future of MS looks bright as the need to identify and quantify with increasing sensitivity and reliability is becoming more urgent whether it be for the purposes of research, regulation, law enforcement or personal use. In this regard a question for the future is whether MS will find a place in our homes and/or workplace environments as a common measuring device for personalized biomedicine and safety. Judging by developments in the last hundred years, perhaps the question should be when? Future developments in MS will not be limited to its primary function as an analytical method. Soft landing MS has become a topic of substantial interest as a technique for material synthesis due to its potential to control the preparation of materials of interest [51-55].

6.3 References

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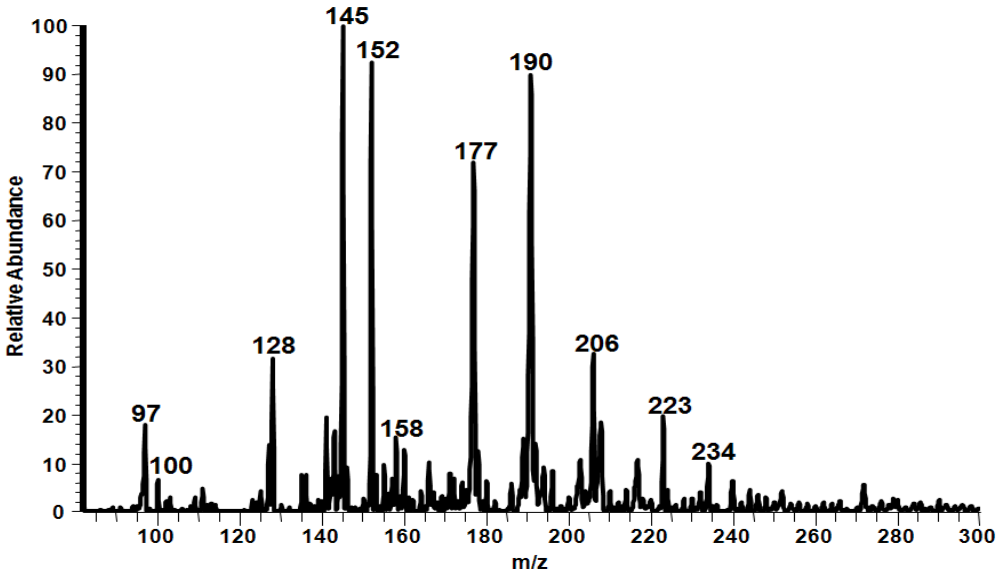
Appendix A

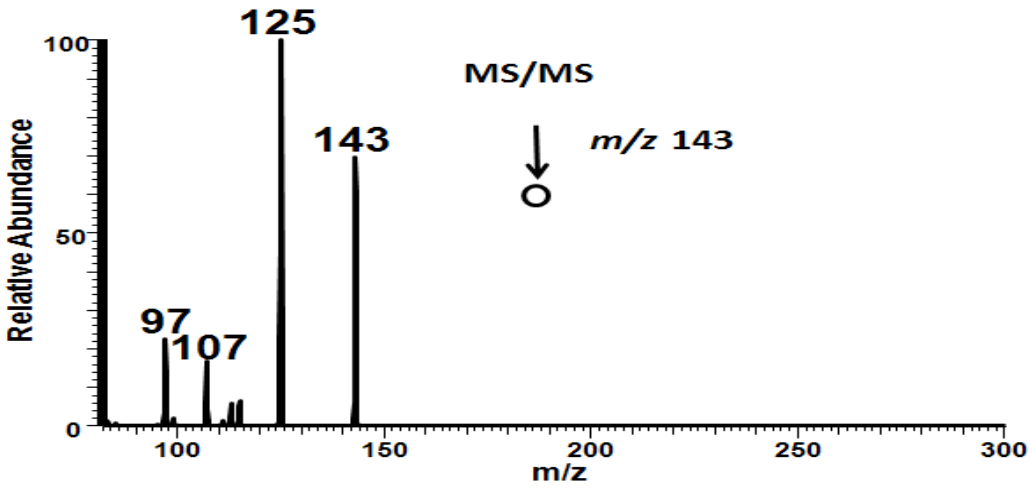
HYDROCARBON ANALYSIS USING DAPCI

1. Analysis gas fuel mixtures with naphthalene reagent at normal temperature

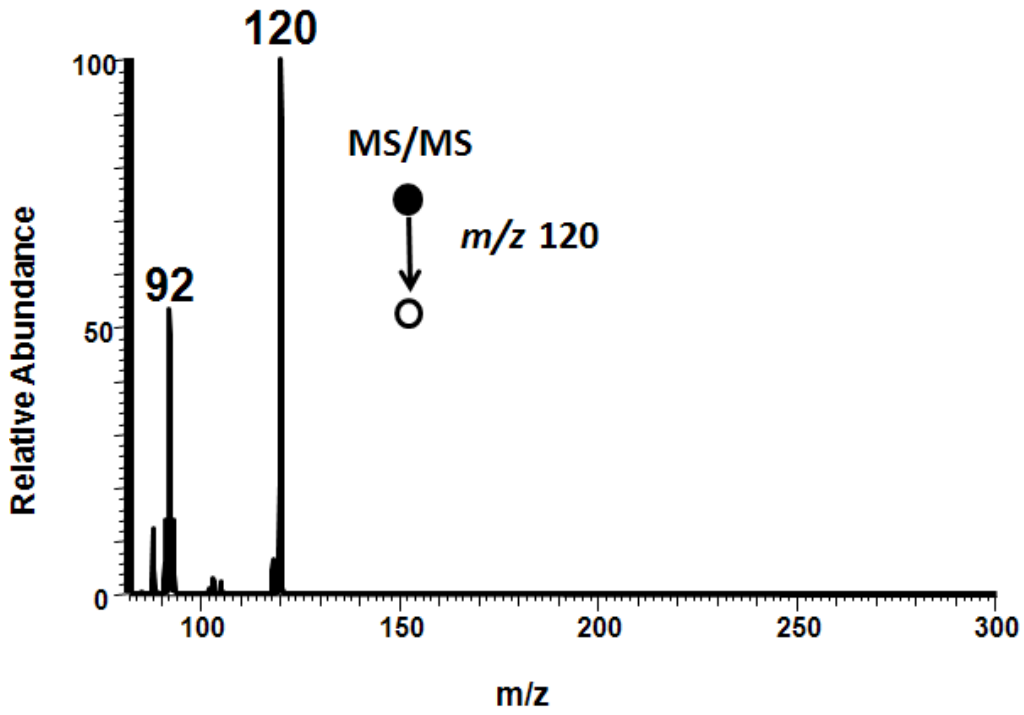


Appendix A.1. DAPCI-MS analysis of gas/diesel standard mixture with naphthalene at normal temperature.

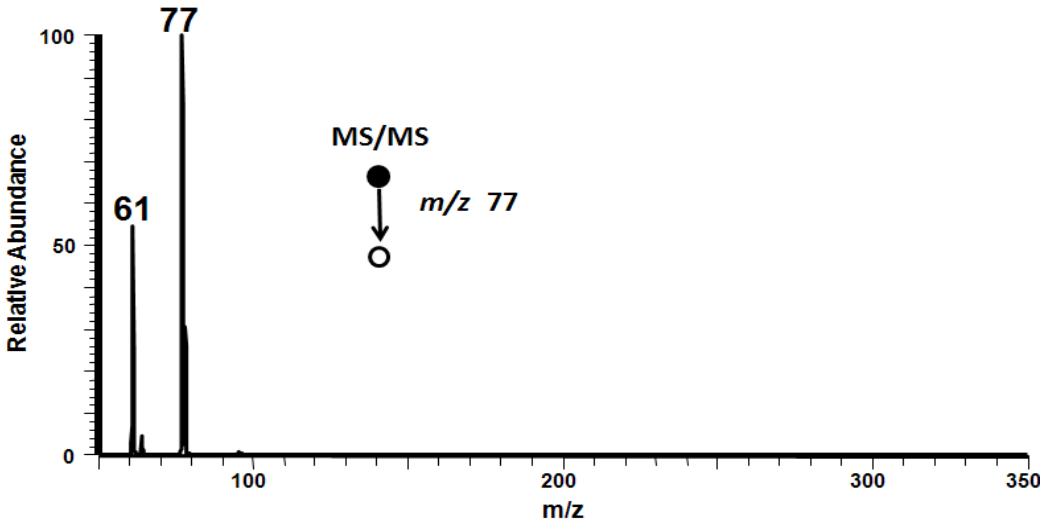
2. DAPCI MS/MS analysis of gas fuel mixtures with naphthalene charge reagent at normal temperature



Appendix A.2. DAPCI-MS/MS analysis at *m/z* 143 of the gas/diesel standard mixture with naphthalene at normal temperature.

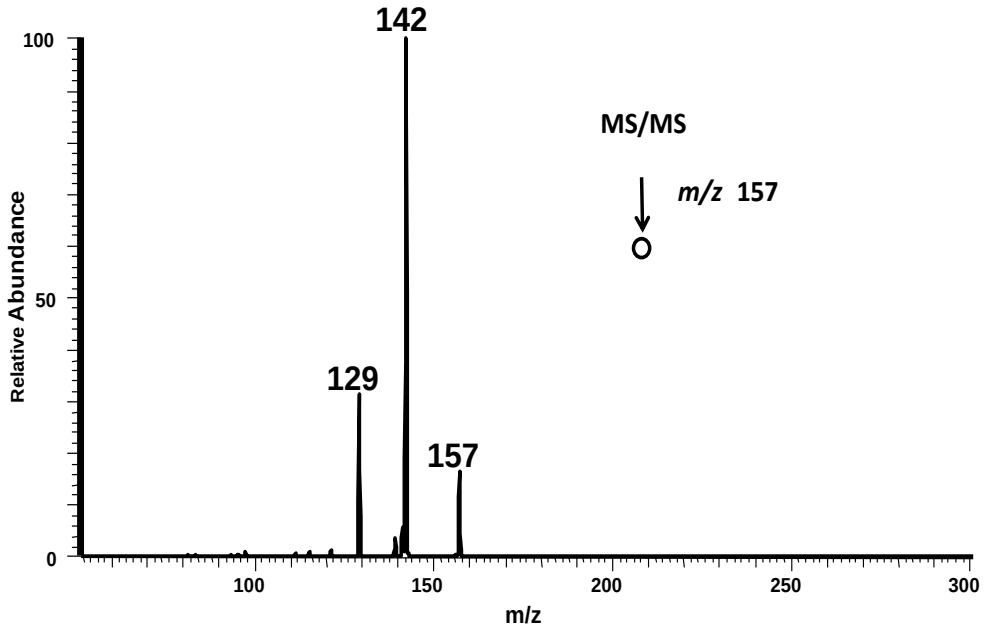


Appendix A.3. DAPCI-MS/MS at *m/z* 120 of the gas/diesel standard mixture with naphthalene at normal temperature.

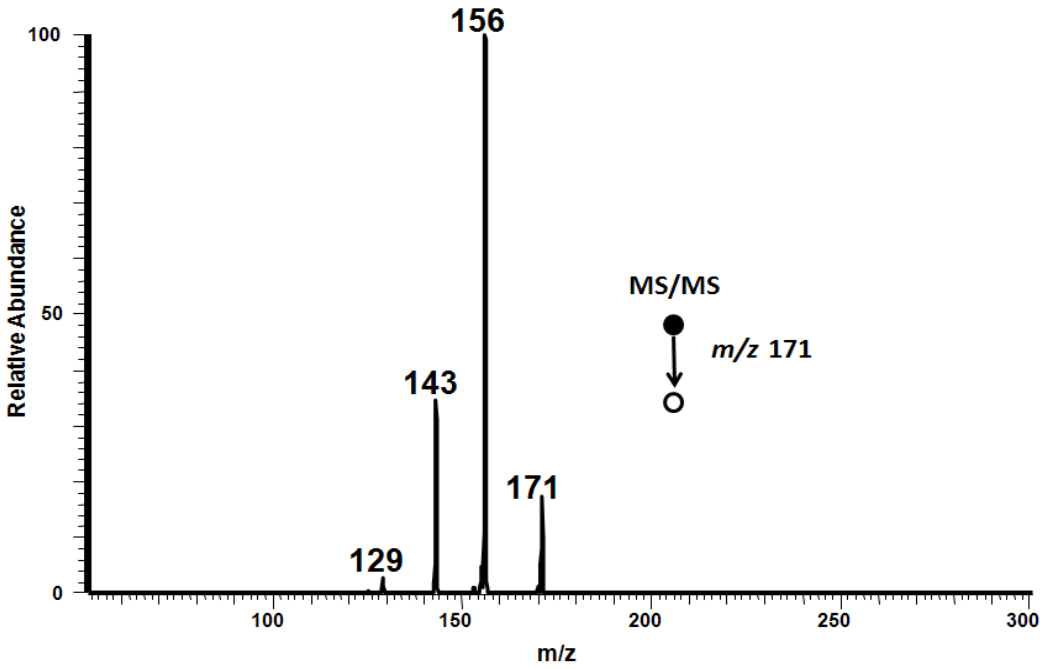


Appendix A.4 DAPCI-MS/MS at m/z 77 of the gas/diesel standard mixture with naphthalene at normal temperature.

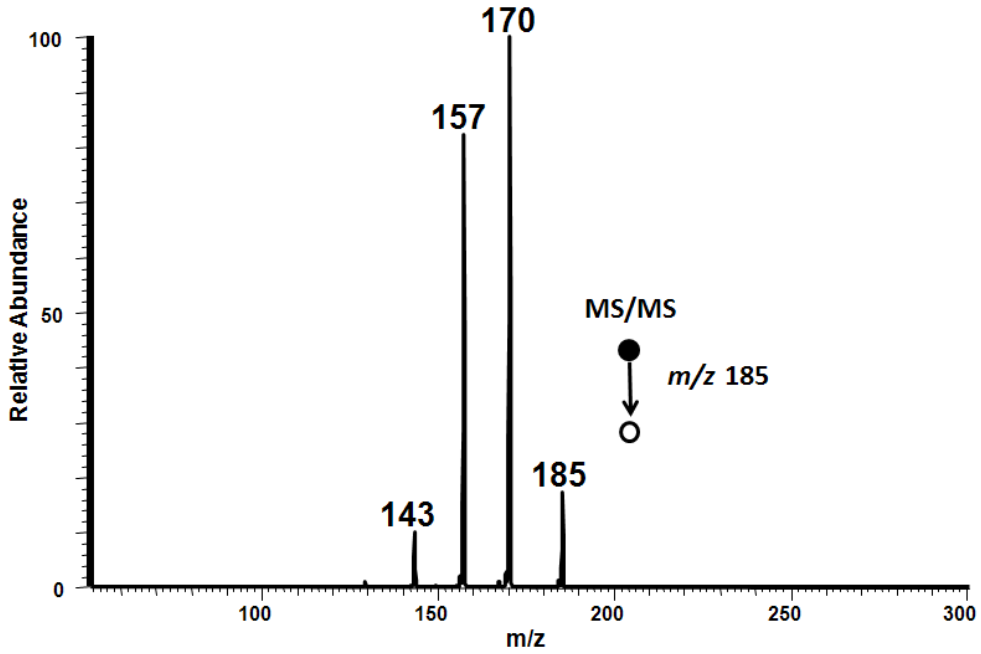
3. MS/MS analysis of gas fuel mixtures with naphthalene charge reagent at 100^{o}C



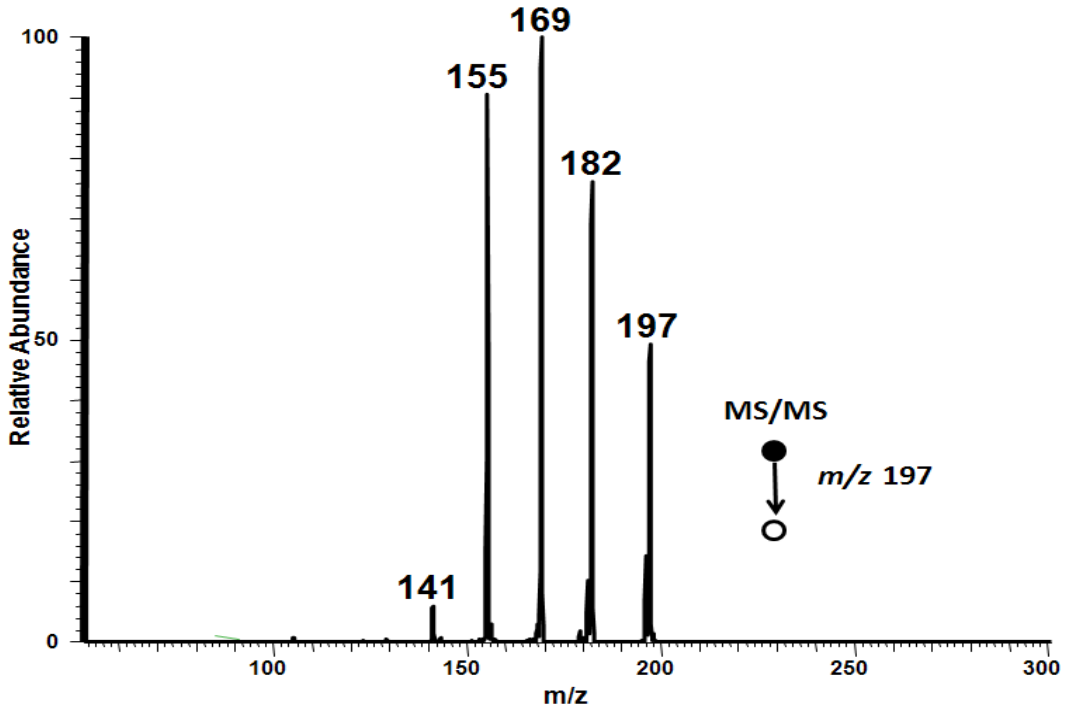
Appendix A.5. DAPCI-MS/MS at m/z 157 of the gas/diesel standard mixture with naphthalene at temperature at 100^{o}C.



Appendix A.6. DAPCI-MS/MS at m/z 171 of the gas/diesel standard mixture with naphthalene at temperature at 100^{o}C.



Appendix A.7. DAPCI-MS/MS at *m/z* 185 of the gas/diesel standard mixture with naphthalene at temperature at 100°C.

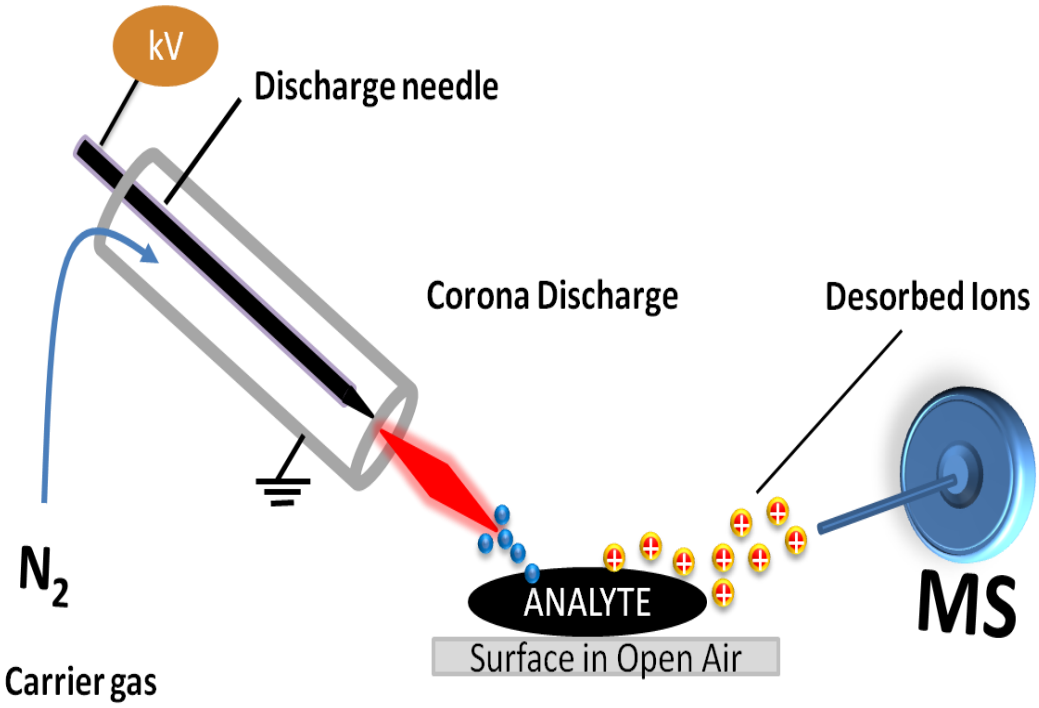


Appendix A.8. DAPCI-MS/MS at *m/z* 197 of the gas/diesel standard mixture with naphthalene at temperature at 100°C.

Appendix B

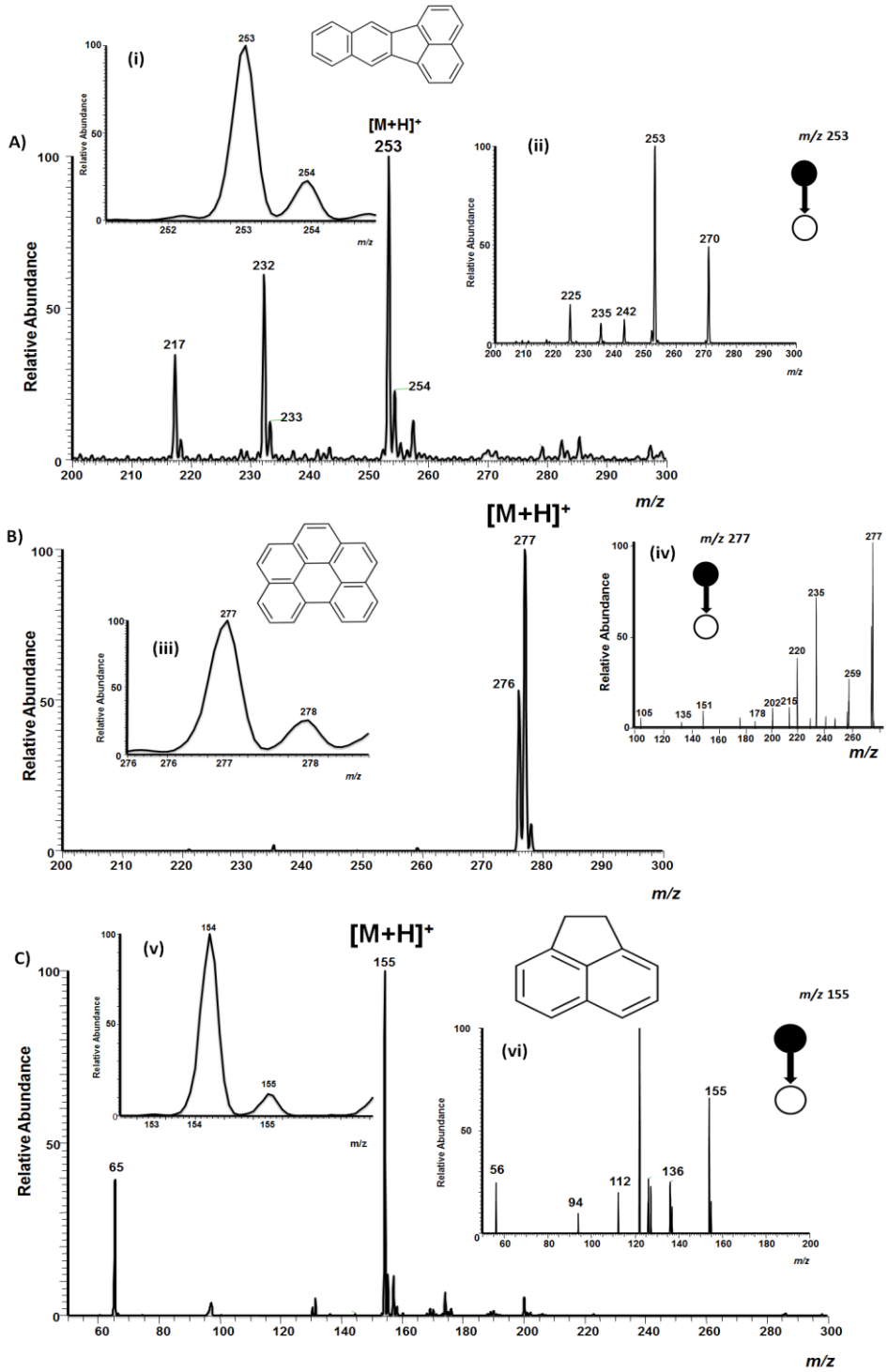
ANALYSIS OF PAHs USING DAPCI ION SOURCE COUPLED TO A PORTABLE MASS SPECTROMETER

1. DAPCI experimental setup for the analysis of alkylated benzenes and PAHs using a commercial mass spectrometer

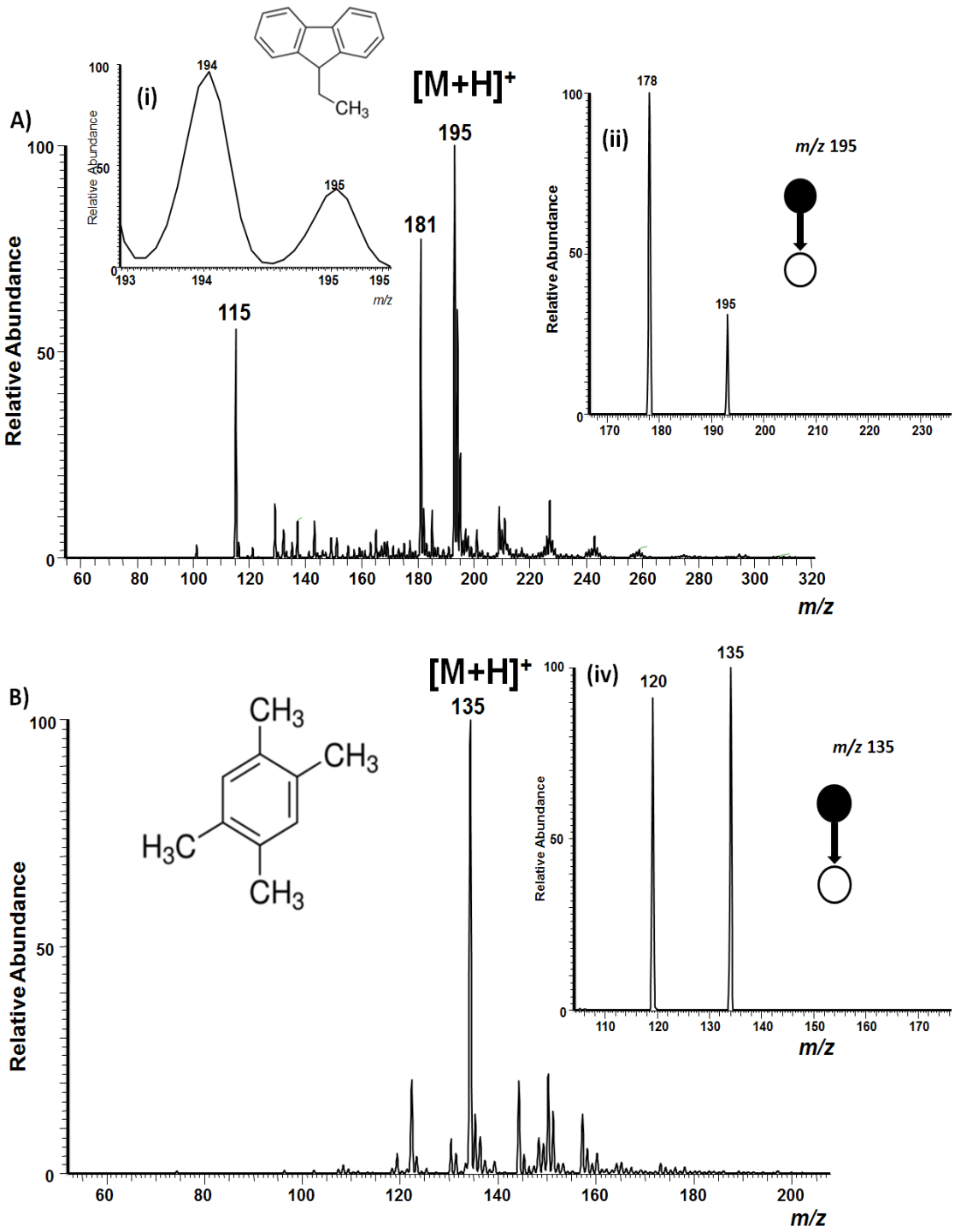


Appendix B.1 Desorption Atmospheric pressure chemical ionisation for direct analysis of alkylated benzenes and PAHs using a commercial bench-top mass spectrometer.

2. Additional PAHs analyzed using a commercial benchtop mass spectrometer

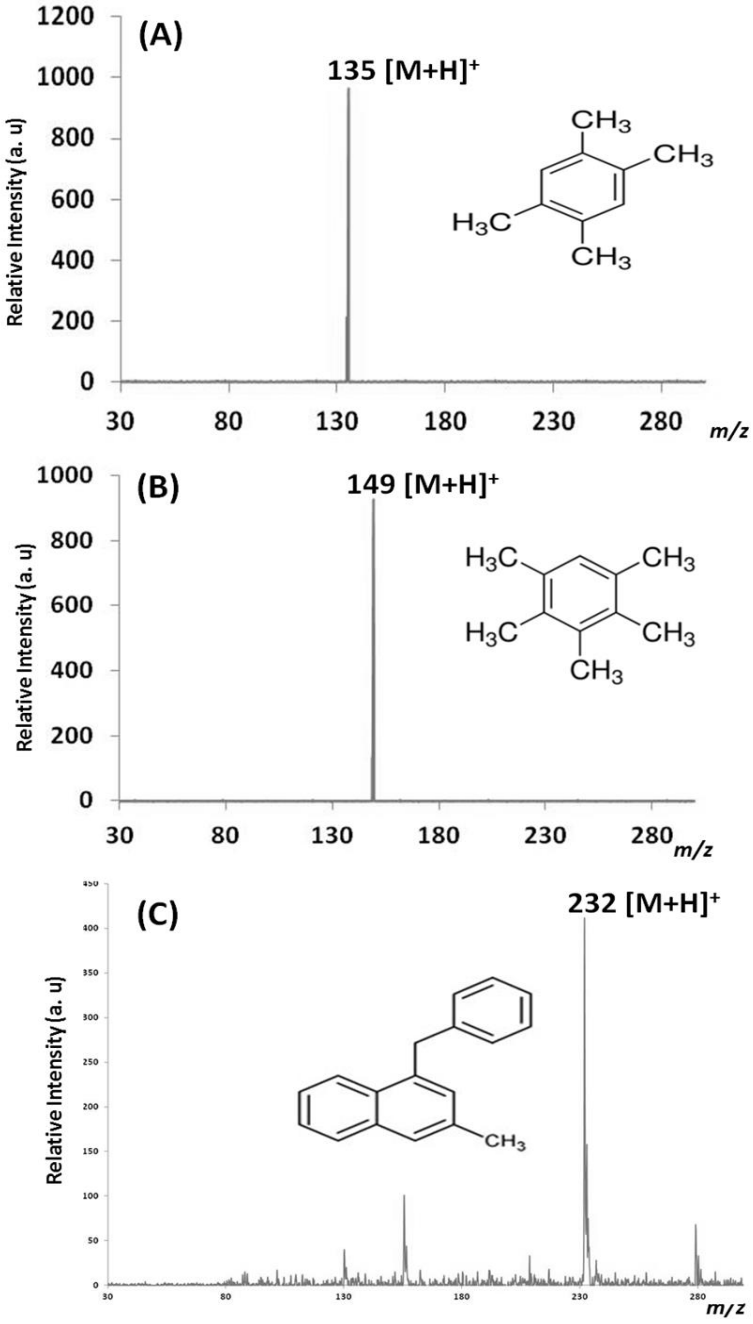


Appendix B.2 Positive ion mode DAPCI mass spectra for non-polar PAHs analysed using a bench-top ion trap instrument. 3 ng μL^{-1} of the analyte(s) in methanol solution was spotted onto the surface and ionised in the open environment by application of an electric potential; (A) protonated benzo[*k*]fluoranthene $[M+H]^+$ (*m/z* 253), (B) protonated indeno[1,2,3-c,d]pyrene $[M+H]^+$ (*m/z* 277) and (C) protonated acenaphthene $[M+H]^+$ (*m/z* 155). Inserts (i), (ii) and (v) shows the isotopic distribution of the analyte ion and insert (ii), (iv) and (vi) show MS/MS CID data for the selected ions using 3 ng μL^{-1} of each analyte in methanol solution.



Appendix B.3. Positive ion mode DAPCI mass spectra for alky substituted benzenes analysed using a bench-top ion trap instrument. 3 ng μL^{-1} of the analyte(s) in methanol solution was spotted onto the surface and ionised in the open environment by application of an electric potential; (A) protonated 9-ethylfluorene $[M+H]^+$ (*m/z* 195), (B) protonated 1,2,3,5-tetramethylbenzene $[M+H]^+$ (*m/z* 135). Inserts (i) shows the isotopic distribution of the analyte ion; insert (ii) and (iv) show MS/MS CID data for the selected ions again using 3 ng μL^{-1} of each analyte in methanol solution.

3. Additional alkylated benzenes analysed using a portable mass spectrometer (mini 10) with DAPCI

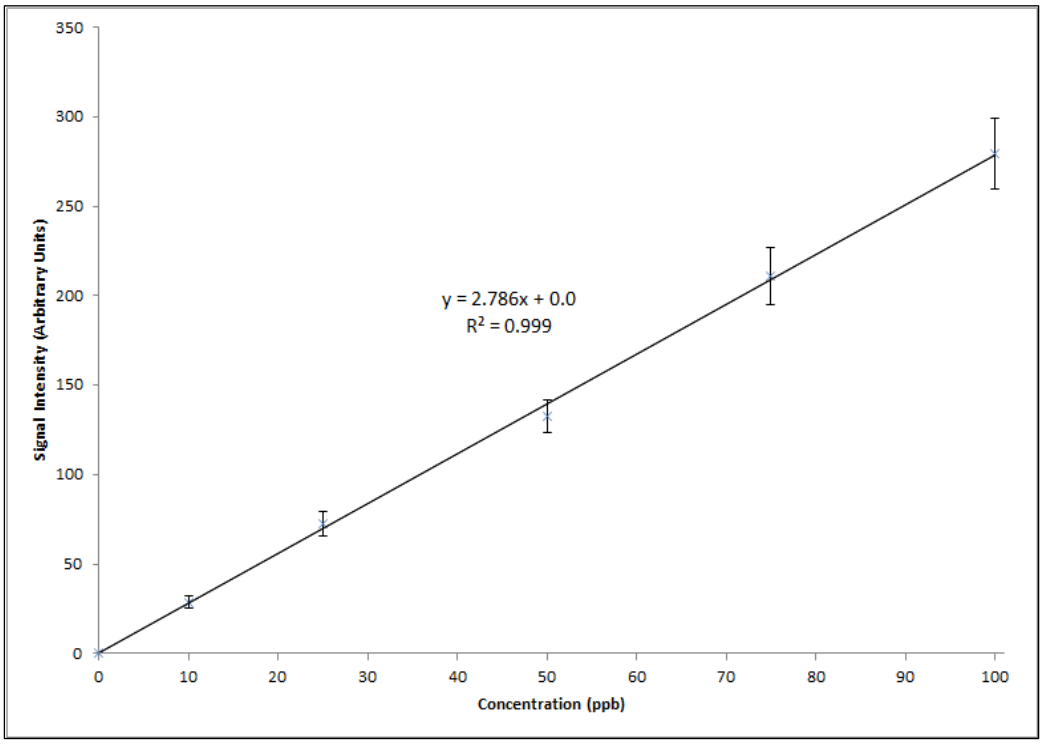


Appendix B.4 Positive ion mode DAPCI mass spectra of alkylated benzenes analysed using DAPCI with a portable instrument. 3 ng μL^{-1} of the analyte(s) in methanol solution was spotted onto the surface and ionised in the open environment by application of an electric potential; (A) protonated 1,2,3,5-tetramethylbenzene $[M+H]^+$ (*m/z* 135), (B) protonated pentamethylbenzene $[M+H]^+$ (*m/z* 149) and (C) protonated benyl-3-methylnapthalene $[M+H]^+$ (*m/z* 232).

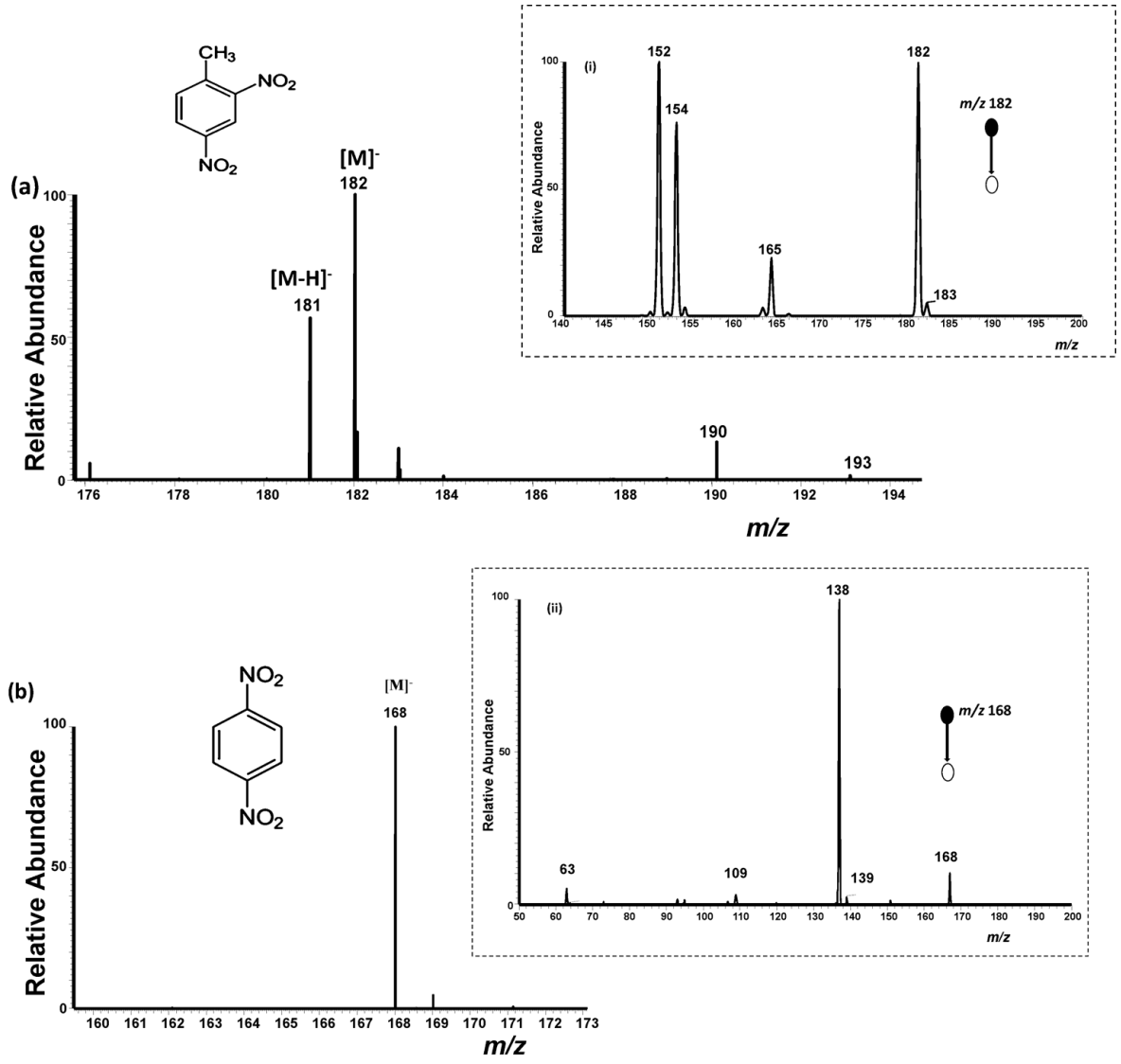
Appendix C

IN-SITU ANALYSIS OF EXPLOSIVES USING A HANDHELD DAPCI ION SOURCE

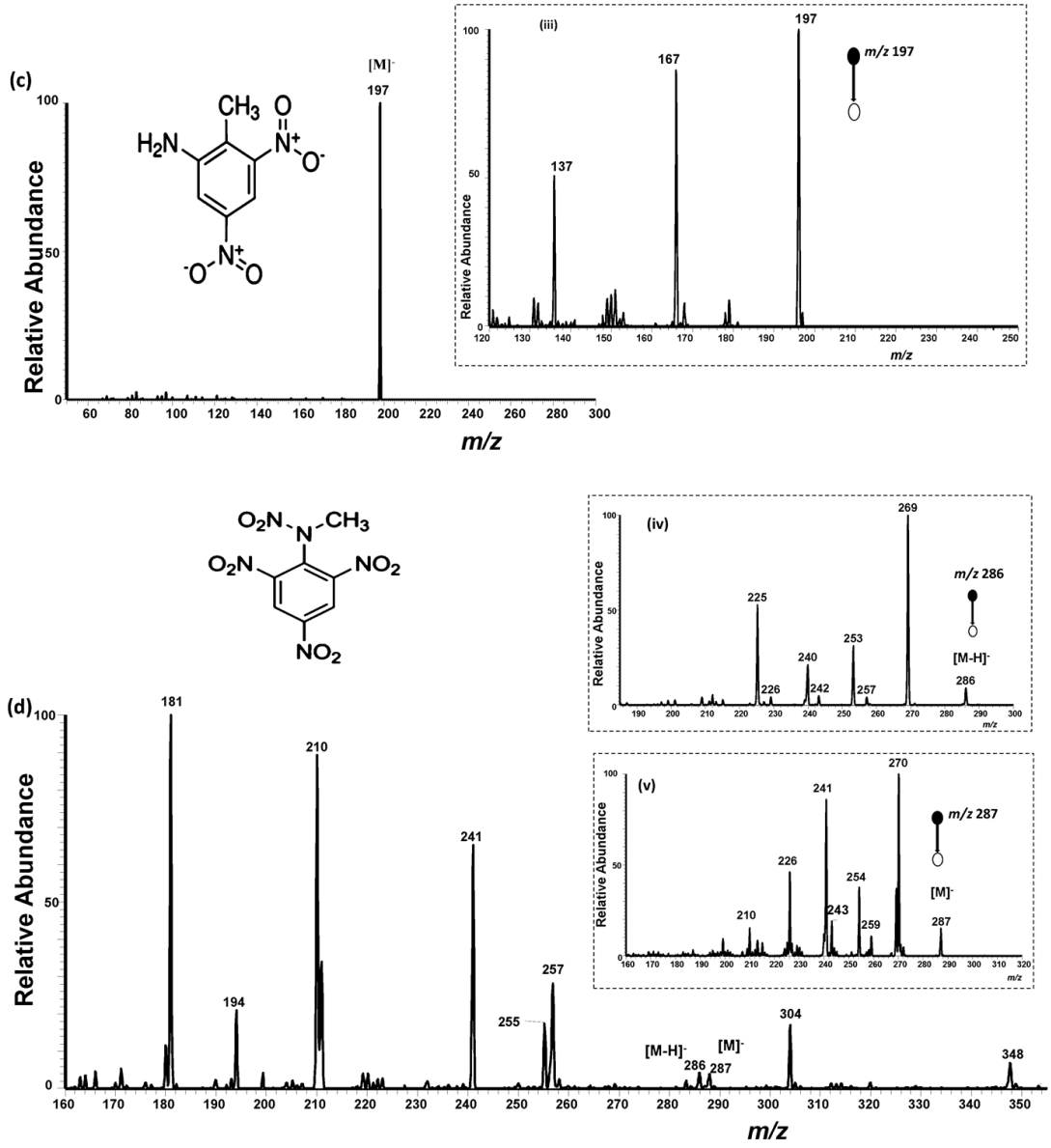
1. Semi-quantitative analysis of the aromatic benzene explosives using a handheld DAPCI ion source



Appendix C.1. TNT calibration curve for the qualitative analysis of nitroaromatic explosives using a handheld DAPCI ion source in the negative ion mode.

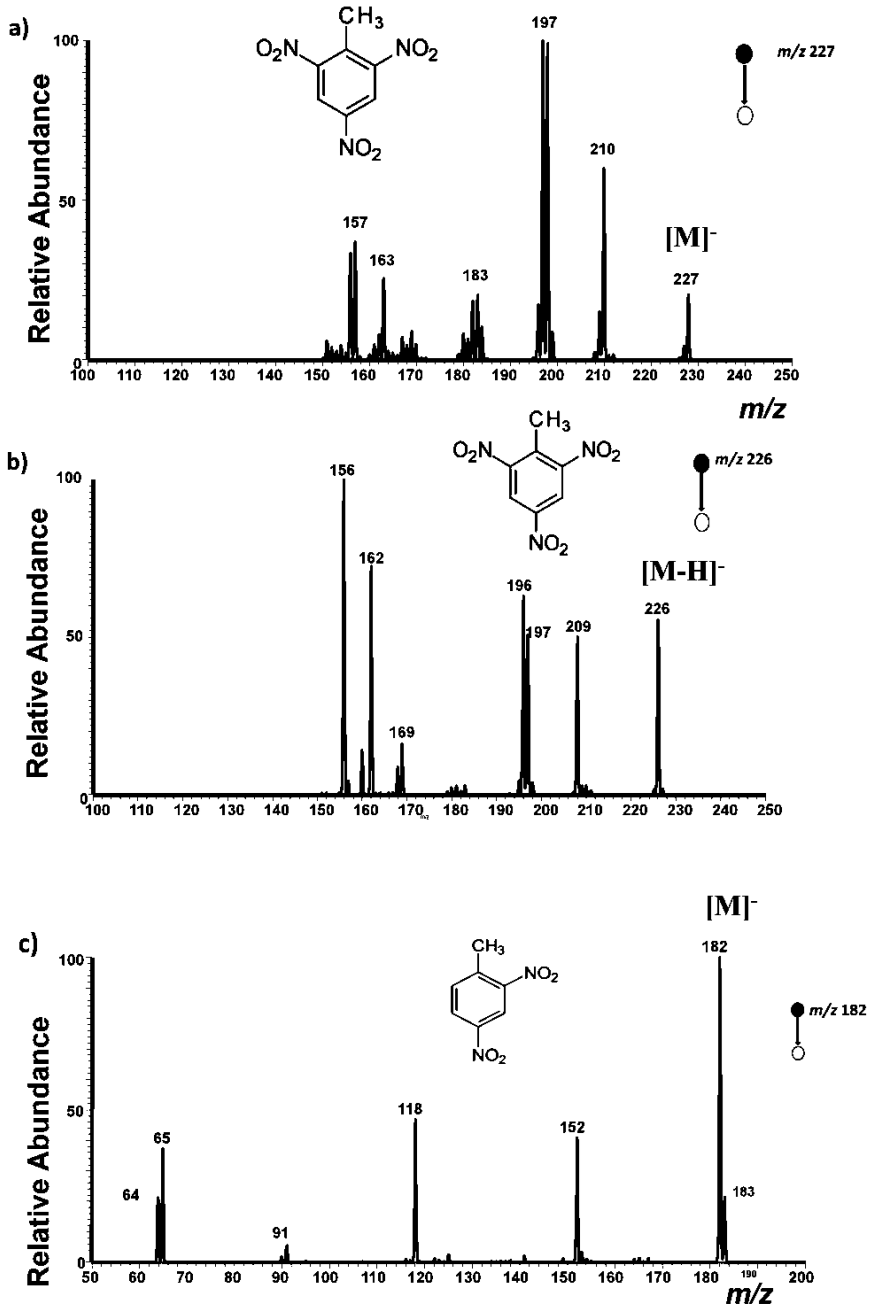


Appendix C.2. Typical handheld DAPCI ion source negative mass spectra obtained using a bench-top ion trap mass spectrometer instrument. 10 pg of 2,4-dinitrotoluene (Mw 182), 1,3-dinitrobenzene (Mw 168) and 2-amino-4,6-dinitrotroluene (Mw 197) model explosive compounds in methanol solution were spotted onto the surface and ionised in the open environment; (a) 2,4-dinitrotoluene molecular anion $[M]^-$ ion (*m/z* 182), (b) 1,3-dinitrobenzene $[M]^-$ (*m/z* 168),



Continuation **Appendix C.2.** (c) 2-amino-4,6-dinitrotroluene molecular anion $[M]^-$ ion (*m/z* 197) and (d) tetryl molecular anion detected from a surface using a handheld DAPCI ion source. Inserts (i)- (iii) show the MS/MS of the molecular anions of; 2,4-dinitrotoluene $[M]^-$ (*m/z* 182), 1,3-dinitrobenzene $[M]^-$ (*m/z* 168), 2-amino-4,6-dinitrotroluene $[M]^-$ ion (*m*/z 197) respectively. While insert (iv) and (v) shows the tandem mass spectra CID data of the deprotonated $[M\text{-}H]^-$ ion at *m/z* 286 and molecular anion $[M]^-$ at *m/z* 287 of tetryl (Mw 287) analysed from a surface using a handheld DACPI ion source.

3. Analysis of nitroaromatic explosives model compounds in a multi component mixture using a handheld DAPCI ion source

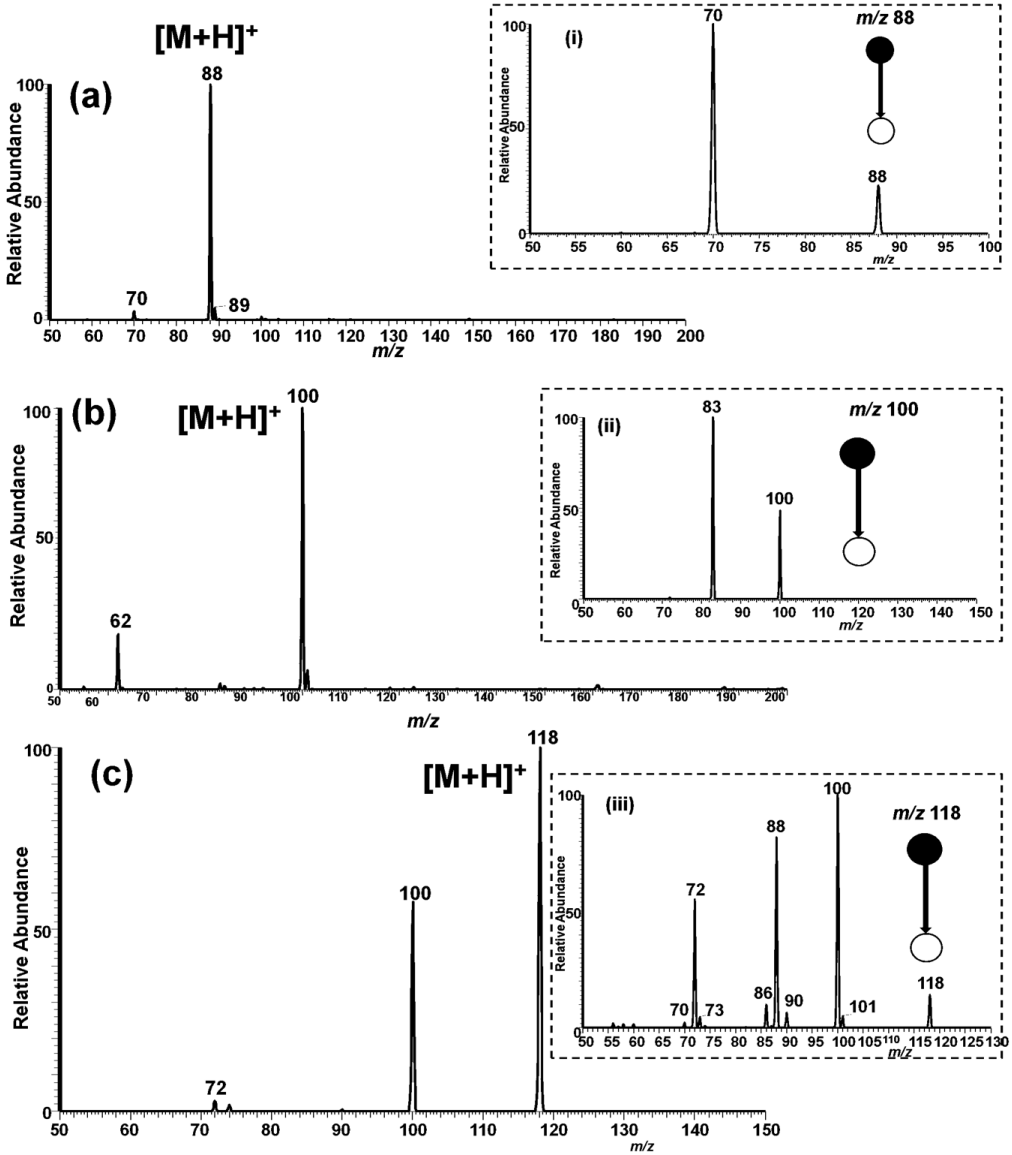


Appendix C.3. Negative handheld DAPCI ion mode mass spectrum for a mixture of several explosive model compounds analysed using a bench-top instrument. 10 pg absolute amounts of each analyte in the mixture were deposited onto the surface and ionised in the open environment by application of an electric potential of -2.5 kV in the negative handheld DAPCI ion mode. Most of the nitrobenzene explosive compounds in the mixture gave intact radical anions $[M]^-$ and deprotonated $[M-H]^-$ peaks. MS/MS CID data for :a) TNT molecular anion $[M]^-$ at *m/z* 227 , b) TNT deprotonated $[M-H]^-$ at *m/z* 226, and c) shows the MS/MS CID mass spectra for 2,4-dinitrotoluene molecular anion $[M]^-$ at *m/z* 182 analysed in the mixture using a handheld DAPCI ion source.

Appendix D

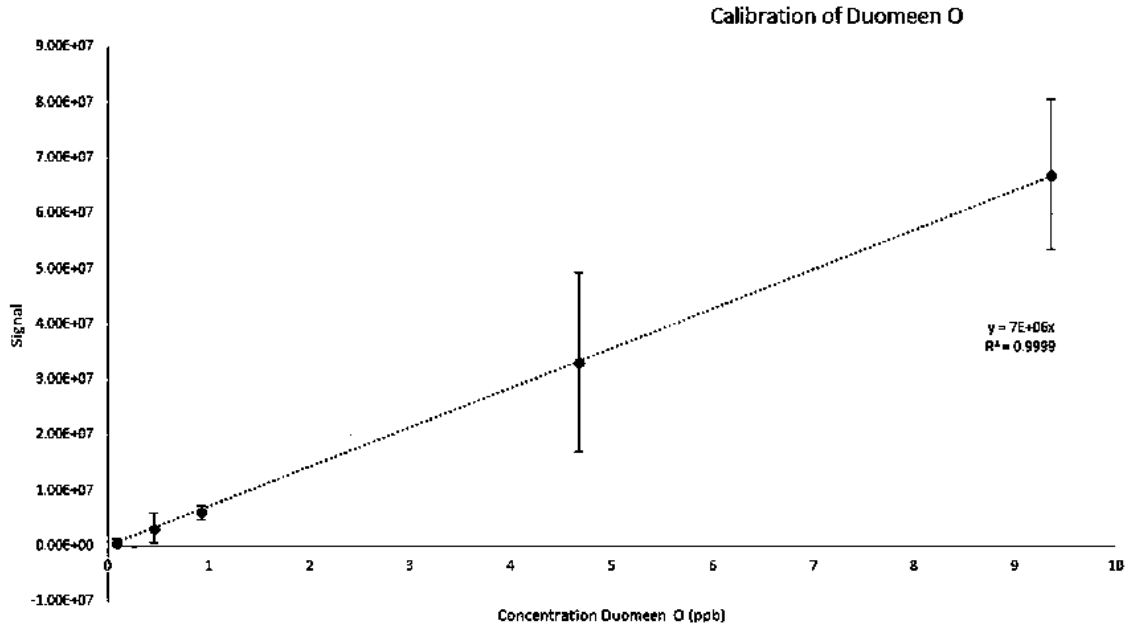
RAPID SCREENING AND QUANTIFICATION OF DUOMEEN® O IN WATER USING PS-MS

1. PS-MS Analysis and identification of Amine Corrosion Inhibitors model compounds



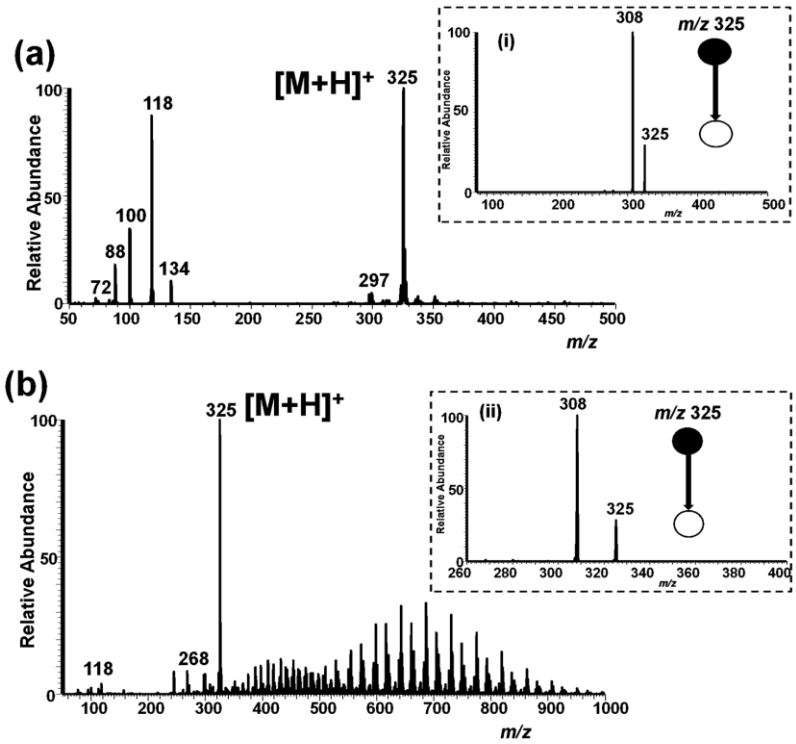
Appendix D.1. Positive ion mode paper spray mass spectrum for amine corrosion inhibitor model compound analyzed using a bench-top ion trap mass spectrometer. Absolute amounts of analyte spotted onto a filter paper and ionised in open air by application of an electric potential, 2 µL, *viz* 10 ppb With methanol spray solvent; (a) morpholine (Mw 87), (b) cycloxylamine (MW 99), c) diethyl amino ethanol (MW 117) Insert (i)-(iii) shows the MS/MS CID data for the selected ions at m/z 88,100 and 118 for morpholine, cycloxylamine and diethyi amino ethanol respectively.

3. Semi-quantitative analysis of the Duomeen O using Paper Spray Mass Spectrometry



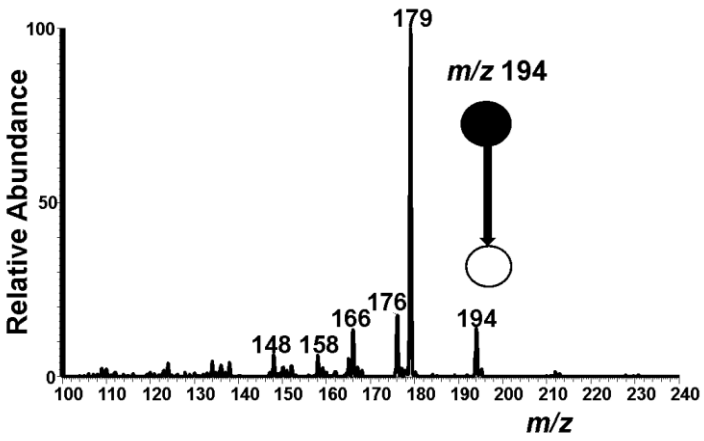
Appendix D.2. Duomeen O calibration curve for the qualitative analysis polydiamine in boiler system water samples using paper spray mass spectrometry in positive ion mode.

4. PS-MS Analysis of Duomeen O in a multi component mixture of polyamine and amine corrosion inhibitor mixtures using paper spray ionisation



Appendix D.3. Positive ion mode paper mass spectrum for polyamine and amine corrosion inhibitor formulation complex mixture analysed using a bench-top mass spectrometer; (a) mass spectrum ascameen corrosion inhibitor mixture, (b) mass spectrum of naylamul S II corrosion inhibitor mixture. Approximately 2 µL of the corrosion inhibitor mixtures was deposited onto the surface and ionised and analysed in the open air by application of an electric potential of + 3.5 kV positive ion mode. Insert (i)-(ii) are the MS/MS CID mass spectra for the *m/z* 325.

4. Characterization of Metaldehyde ammonium ion using PS-MS

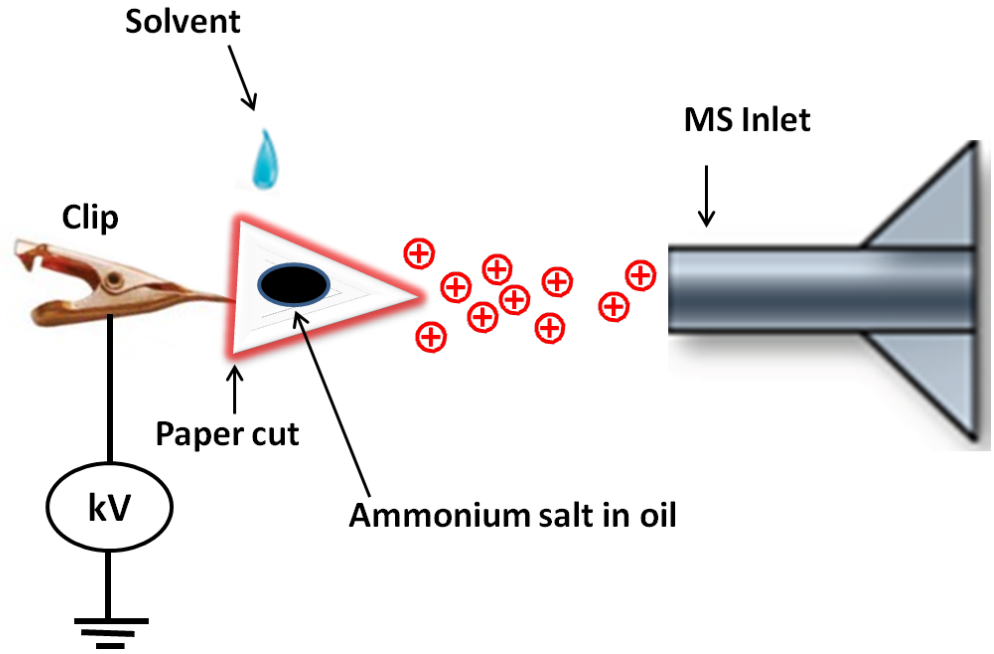


Appendix D.4. Positive ion mode paper spray mass spectrum of metaldehyde recorded using a bench-top ion trap mass spectrometer. 5 µg of the analyte in 1 µL deionized water was spotted onto filter paper and ionized in open air by application of a positive electric potential (3.5 kV) using methanol as the paper spray solvent. The figure shows the CID data for the precursor ion at *m/z* 194.

Appendix E

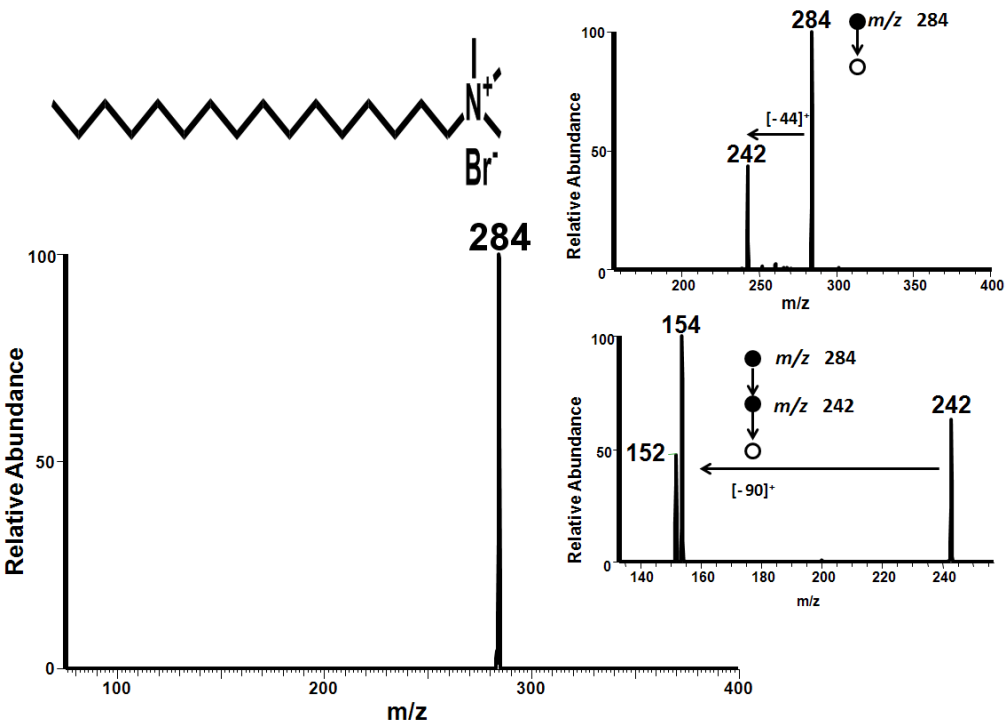
IN-SITU ANALYSIS OF QUATERNERY AMMONIUM CORROSSION INHIBITORS IN PETEROLEUM OIL USING A PORTABLE MASS SPECTROMETER WITH PAPER SPRAY

1. Experimental setup for the analysis of corrosion inhibitors using a bench-top commercial mass spectrometer coupled with paper spray ionisation

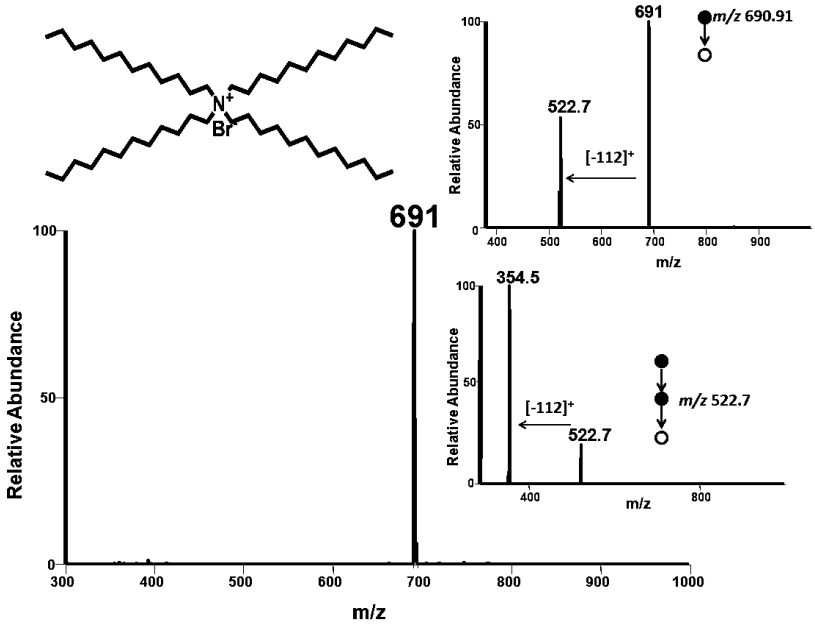


Appendix E.1. Paper sprays mass spectrometry for *in-situ* analysis of corrosion inhibitors using a commercial benchtop mass spectrometer.

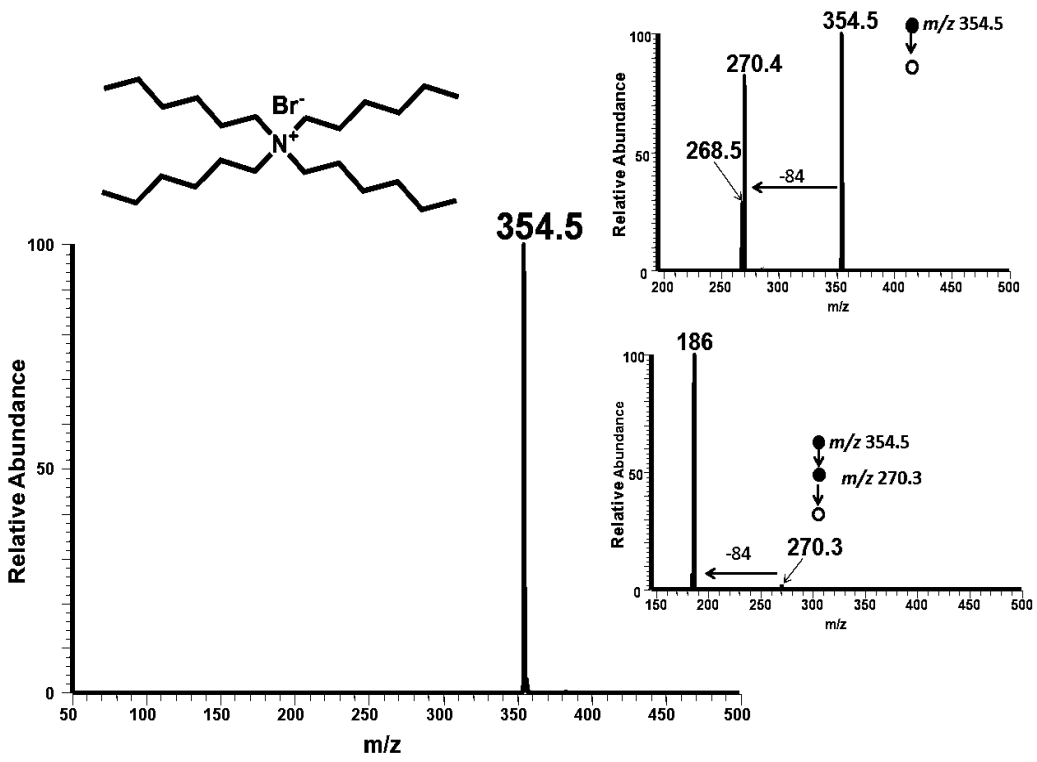
2. Analysis of the corrosion inhibitor model compounds using a bench-top commercial mass spectrometer



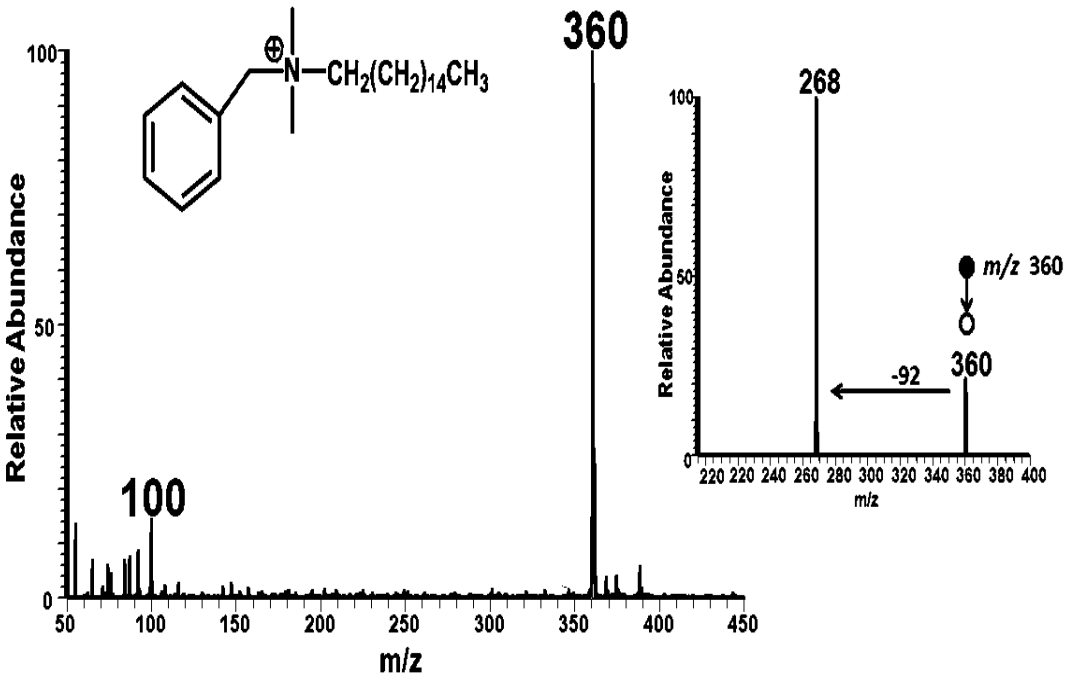
Appendix E.2. Positive PS-MS mass spectrum of hexadecyltrimethylammonium bromide.



Appendix D.3. Positive PS-MS mass spectrum of tetradodecylammonium bromide.

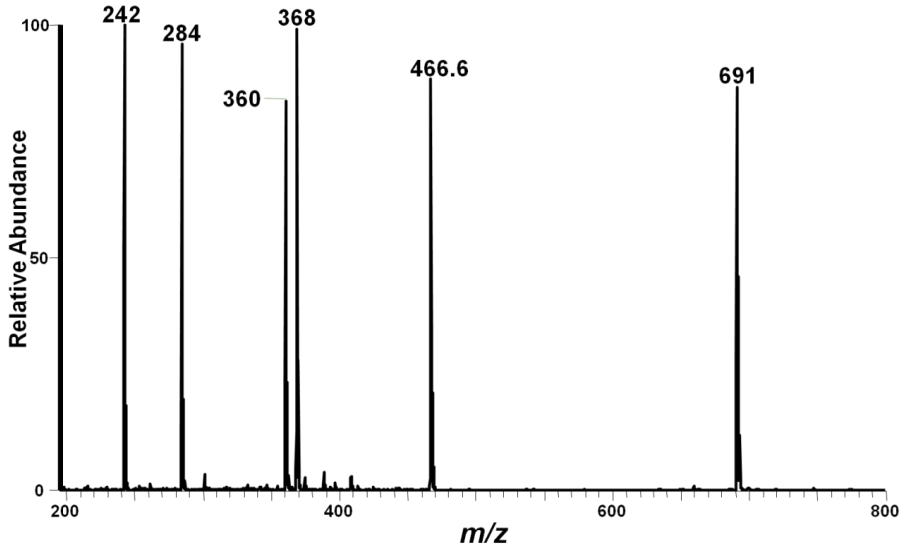


Appendix E.4. Positive ion PS-MS mass spectrum of tetrahexylammonium bromide.

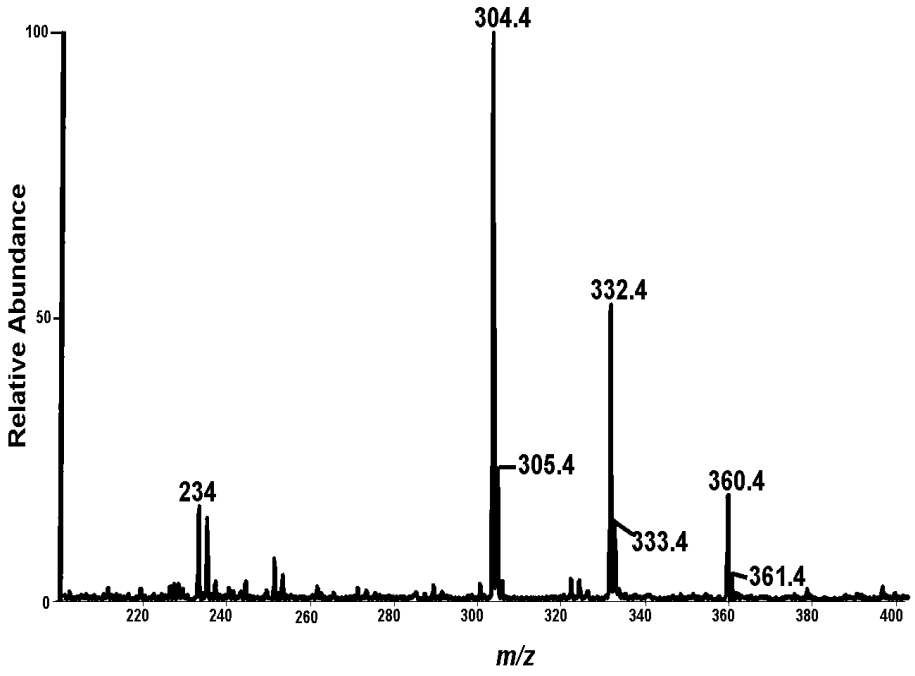


Appendix E.5. Positive ion PS-MS mass spectrum of benylhexadecyldimethylammonium chloride.

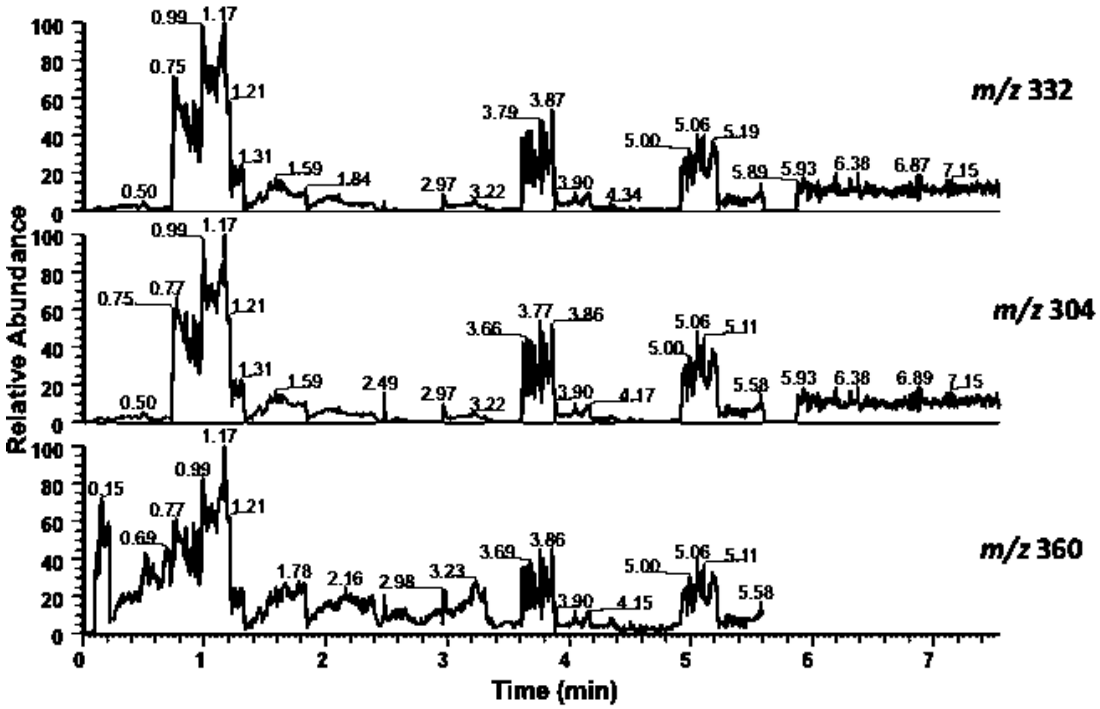
3. Analysis of the corrosion inhibitor model compounds in the oil mixture using a bench-top commercial mass spectrometer



Appendix E.6. Positive ion mode paper spray mass spectrum for artificial mixtures of model compounds analyzed using a benchtop instrument tetrabutylammonium bromide occurs at *m/z* 242, hexadecytrimethylammonium bromide at *m/z* 284, benzylhexadecyldimethylammonium chloride at *m/z* 360, tetraoctylammonium bromide at *m/z* 466.6 and tetradodecylammonium bromide at *m/z* 691.

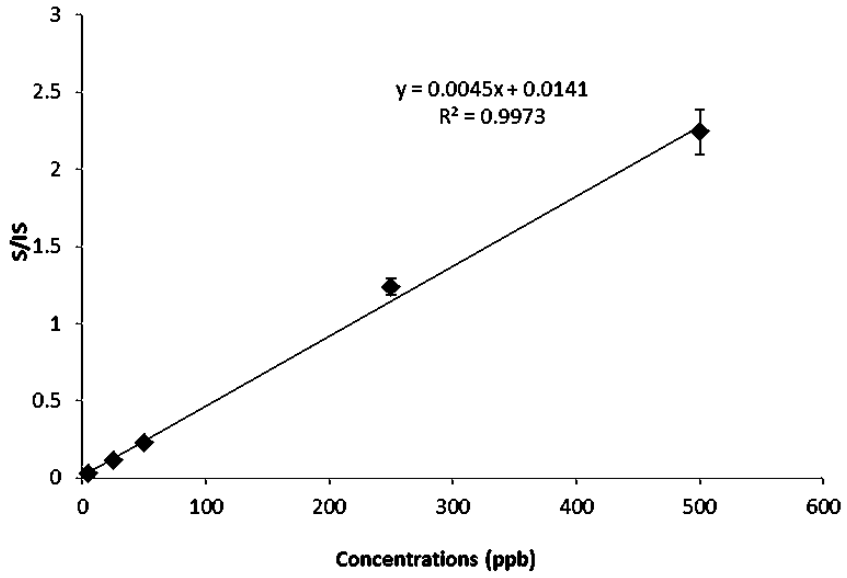


Appendix E.7. Typical positive ion paper spray mass spectra for a mixture of alkyl dimethylbenzyl ammonium chloride salts $[C_6H_5CH_2N\ (CH_3)_2R]Cl$ where R is predominantly n-$C_{12}H_{25}$ (also contains small amounts of *m/z* 332 (C_{14}) and *m/z* 360 (C_{16}) homologs) standard analysed using a benchtop ion trap mass spectrometer. The trace levels of C_{16}, are manifest in the relative abundances compared with other components in the mixture. The total ion chronograms (TIC) do not show *m/z* 360 (C_{16}) which is expected at 5.5 min (Figure S8).



Appendix E.8. Ion chronograms for the for alkyl dimethylbenzyl ammonium chloride $[C_6H_5CH_2N(CH_3)_2R]Cl$ where R is predominantly n-$C_{12}H_{25}$; data for the homologs C_{14} (*m/z*) 332, C_{12} (*m/z*) 304, and C_{16} (*m/z*) 360 are shown**.**

4. Semi-quantitative analysis of quaternary ammonium corrosion inhibitors in petroleum oil



Appendix E.8. Calibration curve for the quantitative analysis of quaternary ammonium salts in oil matrix using a commercial ion trap mass spectrometer.

Appendix F

PUBLICATIONS

Peer-reviewed Journals

1. **Jjunju. Fred. P. M,** Badu-Tawiah, A. K., Li, Anyin, Roqan. Iman and Cooks, R. G; "Hydrocarbon Analysis using Desorption Atmospheric Pressure Chemical Ionisation", Int. J. Mass Spectrom. 345–347, 80-88 (2013).

2. Badu-Tawiah, A. K., Li, A., **Jjunju. Fred. P. M** and Cooks. R. G; "Peptide Cross-Linking at Ambient Surfaces by Reactions of Nanosprayed Molecular Cations", Angew. Chem. Int. Ed., 51: 9417–9421 (2012).

3. **Jjunju. Fred. P. M,** Abraham.K.Badu-Tawiah, Anyin Li, Iman. Roqan and R. Graham. Cooks; "Hydrocarbon Analysis by Desorption Atmospheric Pressure Chemical Ionisation", Prepr.Pap.-Am. Chem. Soc., Div. Energy Fuels Chem. 2012, 57(2).

4. **Jjunju. Fred. P. M,** Badu-Tawiah, A. K., Li, Anyin, Roqan. Iman and Cooks. R. G; "In-situ Analysis of Corrosion Inhibitors using a Portable Mass Spectrometer with Paper Spray Ionisation", Analyst, 2013, 138, 3740-3748.

5. Li, Anyin, **Jjunju. Fred. P. M** and Cooks. R. G, "Nucleophilic Addition of Nitrogen to Aryl Cations: Mimicking Titan Chemistry", J. Am. Soc. Mass Spectrom. (2013) 24(11), 1745-1754.

6. S. Maher, **Jjunju. Fred. P. M**, I. S. Young, B. Brkić and S. Taylor; "Membrane inlet mass spectrometry for *in-situ* environmental monitoring", Spectrosc. Europe 26, (2), pp. 6-8 (2014).

7. **Jjunju. Fred. P. M,** S. Maher, A. Li, H. C. Hsub, P. Wei, S. Taylor and R. G. Cooks; "Ambient analysis of nitrogen compounds in petroleum oil using desorption atmospheric pressure chemical ionisation", Prepr. Pap.-Am. Chem. Soc., Div. Energy Fuels. 59, (2), pp. 753-755 (2014).

8. **Jjunju. Fred. P. M**, S. Maher, A. Li, A. Badu, S. Taylor and R. G. Cooks; "Analysis of polycyclic aromatic hydrocarbons using desorption atmospheric pressure chemical ionisation coupled to a portable mass spectrometer", J. Am. Soc. Mass Spectrom. 26, 271-280 (2015).

9. S. Maher, **Jjunju. Fred. P. M**, and S. Taylor; "Colloquium: 100 years of mass spectrometry: Perspectives and future trends" Review. Modern. Physics. 87, 113-135 (2015).

10. Syed. Sarfaraz, Maher, Simon, Eijkel. Gert; **Jjunju Fred P. M,** Taylor. Stephen, Heeren. Ron; "A Direct Ion Imaging Approach for the Investigation of Ion Dynamics in Multipole Ion Guides", Analytical Chemistry 2015, 87.7: 3714-**3720.**

11. Smith, Ray T, **Jjunju. Fred P M**, and Simon Maher. "Evaluation of Electron Beam Deflections across a Solenoid Using Weber-Ritz and Maxwell-Lorentz Electrodynamics." Progress In Electromagnetics Research 151 (2015): 83-93.

12. **Jjunju Fred P. M,** Maher S, Li A, Syed SU, Smith B, Heeren RM, Taylor S, Cooks RG. Hand-Held Portable Desorption Atmospheric Pressure Chemical Ionisation Ion Source for *in-situ* Analysis of Nitroaromatic Explosives. Analytical Chemistry 2015 Sep 9;87(19):10047-55.

13. **Jjunju. Fred. P. M**, S. Maher, S. U. Syed, R. M. A. Heeren, S. Taylor and Badu-Tawiah, A. K; "Screening and Quantification of Aliphatic Primary Alkyl Corrosion Inhibitor Amines in Water Samples by Paper Spray Mass Spectrometry, Analytical Chemistry 2016 88 (2), 1391-1400.

14. Simon. Maher, **Jjunju. Fred. P. M**, S. Maher, S. U. Syed, R. M. A. Heeren, S. Taylor and Badu-Tawiah, A. K, "Direct Analysis and Quantification of Metaldehyde in Water using Reactive Paper Spray Mass Spectrometry", Submitted to Nature Scientific Reports Analytical Chemistry Journal (March 2016).

Patents

15. Cooks, Robert Graham, **Fred Paul Mark Jjunju**, Anyin Li, and Iman S. Roqan. "Methods of analyzing crude oil." U.S. Patent Application 14/426,879, filed January 23, 2014.

16. **Jjunju. Fred. Paul. Mark**, S. Taylor and Cook, Robert. Graham. "Handheld Portable DAPCI for point and shoot Applications (2016) pending.

Conference Presentations

17. **Jjunju. Fred. P. M**, Badu-Tawiah, A. K., Li, Anyin, Roqan Iman and Cooks, R. G., Hydrocarbon Analysis using Desorption Atmospheric Pressure Chemical Ionisation, 60th American Society of Mass Spectrometry (ASMS) Conference on Mass Spectrometry and Applied Topics, Vancouver, Canada (June 2012).

18. **Jjunju. Fred. P. M**, Badu-Tawiah, A. K., Li, Anyin, Roqan Iman and Cooks, R. G., Hydrocarbon Analysis using Desorption Atmospheric Pressure Chemical Ionisation, 244th American Chemical Society (ACS) National Meeting, Philadelphia, Pennsylvania (August 2012).

19. **Jjunju. Fred. P. M**, Badu-Tawiah, A. K., Li, Anyin, Roqan Iman and Cooks, R. G., Hydrocarbon Analysis using Desorption Atmospheric Pressure Chemical Ionisation, 19th International Mass Spectrometry Conference (IMSC), Kyoto, Japan(September 15 - 21 2012).

20. **Jjunju. Fred. P. M**, Badu-Tawiah, A. K., Li, Anyin, Roqan Iman and Cooks, R. G., Hydrocarbon Analysis using Desorption Atmospheric Pressure Chemical Ionisation, 3rd Asian and Oceanic Mass Spectrometry Conference (AOMSC-3), Kyoto, Japan (September 2012).

21. **Jjunju. Fred. P. M**, Badu-Tawiah, A. K., Li, Anyin, Roqan Iman and Cooks, R. G., Hydrocarbon Analysis using Desorption Atmospheric Pressure Chemical Ionisation, IET/IOP annual meeting University of Liverpool, UK (February 20 2012).

22. **Jjunju. Fred. P. M,** Badu-Tawiah, A. K., Li, Anyin, Roqan Iman and Cooks, R. G., Analysis of Corrsoion Inhibitors using a Portable Mass spectrometer with Paper Spray Ionisation, 6Ith American Society of Mass Spectrometry (ASMS) Conference on Mass Spectrometry and Applied Topics, Minneapolis Minnesota, USA (June 9-13 2013).

23. **Jjunju. Fred. P. M,** Badu-Tawiah, A. K., Li, Anyin, Roqan Iman and Cooks, R. G., Analysis non-basic nitrogen compounds in petroleum oil using desorption atmospheric pressure chemical ionisation, 245th American Chemical Society (ACS) National Meeting, Indianapolis, USA (September, 2013).

24. Li, Anyin, **Jjunju. Fred. P. M,** and Cooks, R. G, Nucleophilic Addition of Nitrogen to Aryl Cations: Mimicking Titan Chemistry, 6Ith American Society of Mass Spectrometry (ASMS) Conference on Mass Spectrometry and Applied Topics, Minneapolis Minnesota, USA. (June 9-13 2013).

25. **Jjunju. Fred P. M**, S. Maher, A. Li, H. C. Hsu, P. Wei, S. Taylor and R. G. Cooks, Ambient analysis of nitrogen compounds in petroleum oil using desorption atmospheric pressure chemical ionisation, RSC Chemistry in the Oil Industry XIII Symposium, Manchester, UK (November 2013).

26. Li. Anyin, **Jjunju. Fred P. M**, S. Taylor and R. G. Cooks, In-situ analysis of oil matrices using paper spray ionisation and portable mass spectrometer: toward chemical analysis in the oil field of corrosion inhibitors and so on, RSC Chemistry in the Oil Industry XIII Symposium, Manchester, UK (November 2013).

27. S. Maher, **Jjunju. Fred P**. M, S. U. Syed and S. Taylor, Performance of a quadrupole gas iiianalyzer operating in stability zones 1 and 3, VS4: 4th Vacuum Symposium UK, Coventry UK (October 2013).

28. Anyin Li, **Jjunju. Fred P. M**, Eric Boone, Robert Shellie, Michael Wleklinski, Kerri A. Pratt, R. Graham Cooks, Paper Spray Ionisation under Harsh Environment and Gas Phase Ion Molecule Reaction under Titan Simulate

Environment, 9th HEMS Workshop 15–18, St. Pete Beach, Florida, USA (September 2013).

29. M. J. Antony Joseph, S. Maher, **Jjunju. Fred P. M**, S. U. Syed, I. S. Young, R. Heeren and S. Taylor, Ion transmission factors affecting sensitivity for a miniature QMS, The 34th BMSS Annual Meeting, Cheshire, UK (April 2014).

30. M. J. Antony Joseph, S. U. Syed, S. Maher, **Jjunju. Fred P. M**, R. Heeren and S. Taylor, Quadrupole mass filter design and performance for operation in stability zone 1, NVMS 50th Anniversary Congress in Rolduc, Netherlands (April 2014).

31. Simon Maher; Sarfaraz U. A. Syed; John R.Gibson, **Jjunju. Fred P. M**, Barry L. Smith; David Taylor; Iain S. Young; Ron M. A. Heeren; and Stephen Taylor; Dog, New Tricks: Enhanced Quadrupole Performance by Addition of a Magnetic Field, 63rd American Society of Mass Spectrometry (ASMS) Conference on Mass Spectrometry and Applied Topics, America's Center, St. Louis, Missouri (May 2015).

32. Simon Maher, Barry L. Smith, Mariya A. Juno, **Jjunju. Fred P. M**, Behnam Bastani, Lei Su, Urszula Salaj-Kosla, Liam Lewis, Jean-Michel Mortz, Dag Hammer, Gyda Cristophersen, Pat O'Leary, Allan MacMaster, Stephen Taylor, Iain S. Young; Making Sense of Water Quality: A Portable MS-UV Sensing Platform for Real-Time Monitoring in Aquaculture, 63rd American Society of Mass Spectrometry (ASMS) Conference on Mass Spectrometry and Applied Topics, America's Center, St. Louis, Missouri (May 2015).

33. Mariya J. Antony Joseph; Simon Maher; **Jjunju. Fred P. M**, S. U. A. H. Syed; John R. Gibson; Iain S. Young; Ron M. A. Heeren; Stephen Taylor; Every Ion Counts: Optimization of the Quadrupole Mass Spectrometer for Improved Ion Transmission and Flat-Top Peaks", 63rd American Society of Mass Spectrometry (ASMS) Conference on Mass Spectrometry and Applied Topics, America's Center, St. Louis, Missouri (May 2015).

34. S.U.A.H Syed; Gert B. Eijkel; Simon Maher; **Jjunju. Fred P. M**, Hans R. Poolman; Stephen Taylor; Ron M.A. Heeren; "There's Plenty of Room at the Bottom: a Micro-Pixelated Position Sensitive Detector for Performance Improvement of a QMS Instrument", 63rd American Society of Mass Spectrometry (ASMS) Conference on Mass Spectrometry and Applied Topics, America's Center, St. Louis, Missouri (May 2015).

35. **Jjunju. Fred. P. M**, S. Maher, A. Li, M. J. Lynch, B. Smith, S. U. Syed, R. M. A. Heeren, S. Taylor and R. Graham Cooks; "Handheld Portable DAPCI Ion Source for in-situ Analysis of Nitroaromatic Explosives" BMSS Annual Conference Birmingham UK (14-17 September 2015).

Academic Honours, Awards and Recognition

36. 03/2016 **Student travel grant**. Royal Chemical Society (GBP 500)

37. 03/2016 **Student Travel grant** IET (GBP 500)

38. 02/2016 **Student travel award,** American Society for Mass Spectrometry (GBP 150).

39. 05/2014 – 03/2015, **Visiting Scholar Appointment**, FOM Institute for Atomic and Molecular Physics, Amsterdam, Netherlands – Prof. R. M. Heeren Investigating QMS ion spatial distributions using a position sensitive detector.

40. 01/2013 – 05/2016, **International Student Research Fellowship,** Department of Electronics and Electrical Engineering, University of Liverpool, UK (Full tuition fee and stipend (GBP > 100,000). *Competitive award based on written proposal and on-site interview*

41. 2014**, Student travel grant,** British Mass Spectrometry Society (BMSS) (GBP 300).

42. 2014**, Student travel grant,** Department of Electronics and Electrical Engineering, University of Liverpool, UK (2014) (GPB 3000).

43. 11/2013 **Best Student Poster,** RSC Chemistry in the Oil Industry XIII Symposium, Manchester, UK (GBP 500).

44. 11/2013 **Student travel grant**. RSC Chemistry in the Oil Industry XIII Symposium (2013) (GBP 200).

45. 05/2013 **Student travel award,** American Society for Mass Spectrometry (2013) (GBP 250).

46. 2009-2010 **King Abdullah University of Science and Technology Fellowship Scholarship** MSc studies (2009–2010) (Full tuition fee and stipend) (Over GBP 100,000).

47. 2009-2010 **King Abdullah University of Science and Technology Fellowship Scholarship** MSc studies (2009–2010) (Full tuition fee and stipend) (Over GBP 100,000).

48. 05/2010 – 09/2010Visiting Scholar Appointment, University of Oxford, UK – Dr D.O'Brien, Developing equalization techniques for high-speed Visible Light Communications using micro pixelated LEDs. (UK living allowances GBP 20,000).

49. 2008-2009 **King Abdullah University of Science and Technology Discovery Scholarship Under graduate studies** (Full tuition fee and stipend) (GBP 45000)

VITA

A native of Uganda, born and raised in Kitovu Nume, a small rural village of Nyendo Masaka district of Uganda East Africa. By the grace of our Lord Jesus Christ, he completed his early education (Primary, O and A Levels) in Masaka. He completed his BSc degree from Makerere University in January 2009. Later in September of 2009, he was awarded a prestigious Discovery Scholarship from King Abdulla University of Science and Technology (KAUST) to study an MSc in Electrical Engineering as discovery scholar. He completed his MSc in December 2010 from KAUST. In March 2011 he was exposed to some basic research work in material disposition and characterization at the optical spectroscopy lab at KAUST under the supervision of Prof. Iman Roqan.

Later on (May 2011) he was appointed as a research associate at the Department of Chemistry, Purdue University (USA) to work on the development of a miniature mass spectrometer with ambient ionisation for in-field applications. Fred spent the first five months of his appointment learning mass spectrometry and gas phase ion chemistry under the guidance of Prof. R. Graham Cooks (Henry B. Hass Distinguished Professor). In 2013 May, he moved to the University of Liverpool Mass Spectrometry group, for his PhD studies, working under the direction of Professor Stephen Taylor. For all the ideas and projects that he was assigned to and those he wished himself, he only successfully completed several of them to international journal publication quality.

His research work led him into several fields including: water analysis, gas phase ion chemistry, oil analysis, and nano science. He is the author of several

papers and patents, and has presented his work at various international conferences, including invited talks for which he won a number of travel grants. He also has conducted collaborative research work on mass spectrometry development for polymer analysis for three months at AMFOF institute of physics Amsterdam the Netherlands, under the guidance of Prof Ron Hereen. Following his recent appointment as postdoctoral fellow at the University of Liverpool, to design and build a miniature mass spectrometer with ambient ionisation for early liver cancer screening. Fred's post-graduation plans are to pursue a leadership career in academia with aspirations of collaborating with the industry to solve 21st century problems.