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SPECIAL FEATURE: PERSPECTIVE

Ion mobility–mass spectrometry

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This review article compares and contrasts various types of ion mobility–mass spectrometers available today and describes their advantages for application to a wide range of analytes. Ion mobility spectrometry (IMS), when coupled with mass spectrometry, offers value-added data not possible from mass spectra alone. Separation of isomers, isobars, and conformers; reduction of chemical noise; and measurement of ion size are possible with the addition of ion mobility cells to mass spectrometers. In addition, structurally similar ions and ions of the same charge state can be separated into families of ions which appear along a unique mass-mobility correlation line. This review describes the four methods of ion mobility separation currently used with mass spectrometry. They are (1) drift-time ion mobility spectrometry (DTIMS), (2) aspiration ion mobility spectrometry (AIMS), (3) differential-mobility spectrometry (DMS) which is also called field-asymmetric waveform ion mobility spectrometry (FAIMS) and (4) traveling-wave ion mobility spectrometry (TWIMS). DTIMS provides the highest IMS resolving power and is the only IMS method which can directly measure collision cross-sections. AIMS is a low resolution mobility separation method but can monitor ions in a continuous manner. DMS and FAIMS offer continuous-ion monitoring capability as well as orthogonal ion mobility separation in which high-separation selectivity can be achieved. TWIMS is a novel method of IMS with a low resolving power but has good sensitivity and is well intergrated into a commercial mass spectrometer. One hundred and sixty references on ion mobility–mass spectrometry (IMMS) are provided. Copyright © 2008 John Wiley & Sons, Ltd.

KEYWORDS: gas phase separation; isomer separation; ion mobility spectrometry; mass spectrometry; electrospray; MALDI; proteomics; metabolomics

INTRODUCTION

During the past decade ion mobility spectrometry (IMS) has come of age as an analytical method.[1–6] Over 50000 stand-alone ion mobility spectrometers are currently employed throughout the world for the detection of explosives, drugs, and chemical-warfare agents. With the development of electrospray[7,8] and matrix-assisted laser desorption ionization[9] as ion sources for IMS, applications have expanded from those limited to vapor-phase samples with volatile analytes to include aqueous and solid-phase samples containing nonvolatile analytes. In addition, the development of high-resolution IMS[10,11] and separations with drift-gas selectivity[12] has enabled the gas-phase separation of structural isomers,[13] polymeric conformers[14] and chiral compounds[15] with speeds never before possible. When coupled with mass spectrometers, IMS, which separates ions on the basis of their size/charge ratios as well as their interactions with a buffer gas, becomes a powerful analytical tool for investigating molecular structure and separating complex samples such as those found in applications of proteomics,[16–18] glycomics,[19–21] and metabolomics.[22]

The coupling of IMS with MS is sometimes referred to as ion mobility–mass spectrometry (IMMS) because the two methods complement and instrumentally match one another so well that they seem to fuse into one analytical measurement. IMMS is not new, but since the demonstration of protein conformer separation by Clemmer *et al.*,[14] applications and instrumental designs of IMMS have been one of the most rapidly growing areas of mass spectrometry. An IMMS instrument must perform five basic processes: Sample introduction, compound ionization, ion mobility separation, mass separation and ion detection. Samples can be introduced into an ion mobility–mass spectrometer in a variety of ways. Vapor samples can be directly introduced or semivolatile compounds can be thermally desorbed from collection filters or traps. Liquid samples are commonly directly infused into the IMMS. Effluents from gas and liquid chromatographs can be

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easily introduced into an IMMS and solid samples can be deposited on sample plates and inserted into an IMMS. Gas-phase ions for IMMS are created by a variety of methods. For vapor samples, the most common ion source is a radioactive ionization (RI) source,[23,24] although corona discharge ionization (CDI),[25,26] photoionization (PI),[25,27] and secondary electrospray ionization (SESI)[28,29] have been used as well. For liquid samples, electrospray ionization (ESI)[30–33] is the method of choice and, for solid samples, matrix assisted laser desorption ionization (MALDI),[34–37] and laser desorption ionization (LDI)[38–40] are common.

Four types of ion mobility spectrometers are used with mass spectrometers: they are drift time,[41] aspiration,[42,43] differential,[44] and traveling wave.[45] Drift-time ion mobility spectrometers are operated under either ambient or reduced pressure conditions. Aspiration and differential ion mobility spectrometers are operated under ambient pressure conditions while the traveling-wave ion mobility spectrometer is operated at reduced pressure. Each of these ion mobility spectrometers can be interfaced to a variety of mass spectrometers. Time-of-flight,[46,47] quadrupole,[48,49] ion-trap,[21] ion-cyclotron,[50] or magnetic-sector mass spectrometers[51,52] have all been used with ion mobility spectrometry. In addition an ion mobility cell can be interfaced to other ion mobility cells or to tandem mass spectrometers to produce IMS^n–MS^m type analyses.[53]

Table 1 lists some of the more common components that have been used in the construction of IMMS instruments. These components are combined in various combinations to produce a variety of ion mobility–mass spectrometers. Given the compatibility of multiple-sampling approaches, ionization methods, ion mobility spectrometers, and mass spectrometers, several configurations are possible for IMMS instruments. Each has unique advantages and disadvantages. Almost all have been investigated and reported in the literature. At least five instrument configurations are available commercially. This review attempts to describe the various types of ion mobility–mass spectrometers which are in use today and to provide insights into the advantages and disadvantages of each instrument for their targeted applications.

Table 1. Components of ion mobility–mass spectrometers

Sample introduction methods	Ionization sources	Ion mobility spectrometers	Mass spectrometers
Vapor introduction	Radioactive ionization (RI)	Ambient-pressure ion mobility spectrometry (APIMS)	Time-of-flight
Thermal desorption	Corona discharge ionization (CDI)	Reduced-pressure ion mobility spectrometry	Quadrupole
Gas chromatography	Photoionization (PI)	Aspiration ion mobility spectrometry (AIMS)	Ion trap
Direct infusion	Electrospray ionization (ESI)	Field-asymmetric ion mobility spectrometry (FAIMS)	Fourier transform ion cyclotron
Liquid chromatography	Secondary electrospray ionization (SESI)	Differential-mobility spectrometry (DMS)	Magnetic sector
Solid samples	Matrix-assisted laser-desorption ionization (MALDI)	Traveling-wave ion mobility spectrometry (TWIMS)	Tandem instruments

ION MOBILITY SPECTROMETRY

Traditional 'drift-time' ion mobility spectrometry (IMS) measures the time that it takes an ion to migrate through a buffer gas in the presence of a low electric field. The primary condition of this low electric field is that the thermal energy supplied from the collisions of the buffer gas is greater than the energy the ions obtain from the electric field. Thus the ions have energies similar to that of the buffer gas and diffusion processes are dominant. Ion mobility under low-field conditions can be thought of as 'directed diffusion.' Under these low-field conditions, the velocity of the ion is directly proportional to the electric field. This proportionality constant is called the ion mobility constant (K) and is related to the ion's collision cross-section[54] by

$$K = \left(\frac{3q}{16N}\right)\left(\frac{2\pi}{kT}\right)^{1/2}\left(\frac{m+M}{mM}\right)^{1/2}\left(\frac{1}{\Omega}\right)$$

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where q is the charge on the ion, N is the number density of the buffer gas, k is the Boltzmann's constant, T is the absolute temperature, m is the mass of the buffer gas, M is the mass of the ion, and Ω is the collision cross-section of the ion. Traditional 'drift-time' ion mobility spectrometry is the only type of IMS in which collision cross-sections of ions can be measured directly from the drift time. (Note: because 'drift-time' ion mobility spectrometry was the first and still is the most common type of ion mobility spectrometry, it is referred to simply as IMS rather than DTIMS.)

Two modes of operation have been developed for obtaining drift-time ion mobility spectra: reduced-pressure ion mobility spectrometry (RPIMS) and ambient-pressure ion mobility spectrometry (APIMS). The historical approach for obtaining mass-identified mobility data was to position a mobility cell within the MS vacuum and increase the pressure in the region of the IMS cell to a few torr.[46,55,56] The primary advantage of the reduced pressure IMS (RPIMS) approach is the efficient transfer of ions from the mobility cell to the mass spectrometer. RPIMS may also be used when collision cross-section measurements are desired for mass-selected ions. In this configuration, the IMS cell is positioned after the mass spectrometer, where the mass-selected ions are introduced into the mobility cell.[57,58] Energy dependence of ion conformation, fragmentation, and ion-molecule reaction can also be investigated with the mass selection of ions prior to their mobility separation and drift-time measurement.

Ambient pressure IMS (APIMS) has historically been used as a field-deployable stand-alone analytical instrument for the separation and detection of trace quantities of explosives, drugs, and chemical warfare agents; and as a detector for gas, liquid and supercritical fluid chromatography.[6,59–65] When interfaced to a mass spectrometer it has the general advantage over RPIMS cells of higher resolving power and greater separation selectivity but suffers from lower sensitivity due to inefficient transfer of ions from ambient pressure into the vacuum of the mass spectrometer.[2,10]

The common disadvantage of both RPIMS and APIMS is that, in order to achieve separation, a narrow pulse of ions must be periodically introduced into the drift region, creating a duty cycle which decreases the sensitivity of the instrument.[66]

Continuous introduction of ions into an ion mobility spectrometer can be accomplished, however, by directing the flow of buffer gas perpendicular to the direction of the electric field.[67–69] The ions are introduced with the buffer gas into the electric field such that they are directed orthogonally to the gas flow and onto a series of segmented electrodes. Ion mobility is measured as a function of the distance they travel through the buffer gas before impinging on an electrode. Both positive and negative ions can be measured simultaneously since they travel in opposite directions and are collected on the two sets of opposing segmented electrodes. Commercially, this type of IMS is called an aspiration ion mobility spectrometer and is also known as the IMCell.

In an alternate method for introducing ions continuously into an ion mobility spectrometer, ions are passed between two flat parallel electrodes or two concentric cylinder electrodes with a flowing buffer gas similar to the aspiration IMS design.[70–73] Unlike the IMCell design, the electrodes are not segmented and an alternating electric field is placed between the two electrodes such that the ions move perpendicular to the gas flow in alternating directions. In one direction (A) the field is twice as strong but is applied for only half the time as it is in the opposite direction (B). Unlike the traditional mode of operation, a high electric field is applied between the electrodes such that the ion's mobility is no longer directly proportional to the electric field. Thus when the ion is traveling in the A direction, it travels with a different mobility than in the B direction. It is this difference in mobilities between the two fields which the instrument uses to separate the ions. As the ions flow between the two electrodes they are dispersed according to their differential mobility. Thus, the voltage used to create the alternating field is called the dispersion voltage (DV). To focus ions through the electrodes and into a mass spectrometer, a compensation voltage (CV) is applied to one of the electrodes. As the CV is scanned, ions with characteristic differential mobilities are detected in the mass spectrometer. If the traditional drift-time method for ion mobility spectrometry is analogous to time-of-flight mass spectrometry then the differential-mobility method is analogous to quadrupole mass spectrometry. Alternating-field ion mobility spectrometry (AFIMS) has been called field-ion spectrometry (FIS), field-asymmetric waveform ion mobility spectrometry (FAIMS) and differential-mobility spectrometry (DMS). FAIMS and DMS are the most common names used to refer to this mode of mobility spectrometry. In this review DMS will be used as a general term for differential-mobility spectrometry and IMS will be used to denote the drift-time mobility separation.

A novel method of ion mobility that has recently been developed and introduced commercially is called 'traveling-wave' ion mobility spectrometry (TWIMS).[74,75] In this design, construction of the mobility cell is similar to that of a traditional segmented IMS. Unlike the traditional IMS, in which a low electrical field is applied continuously to the cell, a high field is applied to one segment of the cell and swept sequentially through the cell one segment at a time in the direction of ion migration, separating ions based on their mobility. Thus ions are moved through the mobility cell in pulses as waves of the electrical field pass through them.

Each IMS design has unique ion mobility characteristics and advantages when coupled with mass spectrometers. The traditional drift-time IMS provides the highest resolving powers, but has a decreased sensitivity due to its low duty cycle. Most traditional IMS instruments are operated at ambient pressure but when interfaced to a mass spectrometer, reduced-pressure ion mobility spectrometers (RPIMS) offer the possibility of ion focusing, improving ion-transport efficiency of the mobility tube and ease of interface to mass spectrometers. Higher pressures have the advantage of more ion-molecule interactions per second and thus greater separation selectivity.

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The continuous-ion introduction systems of the aspiration and the alternating-field IMS are operated at ambient pressures and provide higher sensitivity than the drift-time approach. However, these spectrometers have lower resolving powers than the drift-time IMS instruments. When operated in a noncontinuous mode (i.e. voltages are scanned to monitor a range of mobilities) sensitivity is also reduced due to the duty cycle of the scan. Because high-field DMS instruments separate ions on the basis of mobility differences between two electrical fields, they provide more orthogonal information to mass than that of a drift-time IMS.[76]

The TWIMS is operated at reduced pressures and has the lowest resolving power of all the ion mobility spectrometers. However, this system is in the early stages of development and evaluation. Resolving powers will undoubtedly improve as more is understood about this complex but unique mobility cell. In addition, high-field operation may lead to improved separation selectivity. When coupled to a high-resolution mass spectrometer, ion mobility resolving powers do not have to be high to provide useful size separations of isobars.

For more detailed information on the theory and operation of ion mobility spectrometers, the reader is referred to the text by Eiceman and Karpas.[77]

EARLY-ION MOBILITY–MASS SPECTROMETRY

The father of ion mobility–mass spectrometry is undoubtedly E. W. McDaniel from the Georgia Institute of Technology. During the 1950s and 1960s, he developed low field drift cells to study ion mobilities and ion molecule reactions in gases. In an attempt to settle an argument over the terminal ion species produced in hydrogen, he coupled his low-field ion mobility drift cell to a magnetic sector mass spectrometer.[55] Time-of-flight[46,78,79] and quadrupole mass spectrometers[80,81] rapidly replaced magnetic-sector instruments for the mass measurement of mobility-separated ions. Most of the early mobility experiments were conducted at reduced pressures ranging from 0.1 to 10 torr. By the 1970s, however, a commercial IMMS was available based on an ambient pressure ion mobility spectrometer interfaced to a quadrupole mass spectrometer.[82] Throughout the 1970s and 1980s ion mobility–mass spectrometry was dominated by the use of mass spectrometry to identify mobility selected ions from ambient pressure ion mobility spectrometers.[83,84]

The development of modern instrumentation using ion mobility for the investigation of gas-phase ion structure stems from the work of Jarrold *et al.*,[85] and Kemper and Bowers.[86] They modified an early IMMS design of Bohringer and Arnold[87] to measure the mobility of mass-selected ions that were injected into drift cells at reduced pressures (1–10 torr). While initially focused on the studies of ion-neutral reactions of ion clusters and metal ions, mass-selected mobility studies have become a fertile experimental approach for investigating gas-phase ion structures of a variety of molecules including those of proteins, peptides, nucleic acids and carbohydrates.

MODERN ION MOBILITY–MASS SPECTROMETERS

Today there are a variety of ion mobility–mass spectrometers. The most common are drift-time IMS and DMS systems interfaced to time-of-flight, quadrupole, ion trap and FTICR mass spectrometers. Each is briefly described below along with their salient features and applications. Unfortunately, there is not enough time in this short review to detail all designs and applications but the few selected examples demonstrate the analytical power which results from coupling mobility with mass measurements.

Ion mobility (time-of-flight) mass spectrometry [IM(tof)MS]

The workhorse of ion mobility–mass spectrometers is an IMS coupled to a time-of-flight mass spectrometer. Figure 1 is a schematic diagram of a typical ion mobility (time-of-flight) mass spectrometer design commonly used today and first described by McAfee *et al.*[46,47] Various components include (1) an electrospray ionization (ESI) source, (2) an ESI interface to the ion mobility spectrometer, (3) a desolvation chamber where the electrospray solvent is evaporated, (4) an ion gate which pulses packets of ions into the drift region, (5) the drift region where ions are separated according to their mobility, (6) a pinhole interface to vacuum, (7) transfer and focusing ion lenses to move the ions from high pressure to low pressure and (8) a reflectron time-of-flight mass spectrometer which separates ion on the basis of their mass/charge ratio. Because IMS spectra are obtained in milliseconds and time-of-flight mass spectra are obtained in micro-seconds, thousands of mass spectra can be obtained for each ion mobility spectrum producing a two-dimensional array in which both mobility and mass of ions are recorded.

One unique feature of IMMS spectra is that they often exhibit a mass-mobility correlation for classes of ions. These mass-mobility correlations are commonly called 'trend lines'. There are two conventions for plotting IMMS spectra. In one case, mass is plotted as a function of drift time (or collision cross-section) and in the other case, drift time (or collision cross-section) is plotted as a function of mass. In either case trend lines are observed. Ions of a given class often follow a trend line but can vary from that line. In a study of peptides this variation was as large as 10%.[88] For classes of compounds where structures are dissimilar, larger variation may occur. When mass is plotted as a function of drift time (or collision cross-section), ions falling above the trend line are more 'dense' than the average ion in that class (i.e. they are more tightly folded) and, conversely, denser ions of a class fall below the trend line when drift time (or collision cross-section) is plotted as a function of mass.

Figure 2 shows a two dimensional mobility-mass spectrum for intracellular metabolites extracted from an *E-coli* culture.[22] Random noise is distributed throughout the 2D space, increasing the signal/noise ratio of the metabolite response over that which would be observed in one dimension. Over 1000 metabolite peaks are observed in this spectrum with 42 isobaric pairs identified. The spectrum on the top margin is the mass spectrum integrated across

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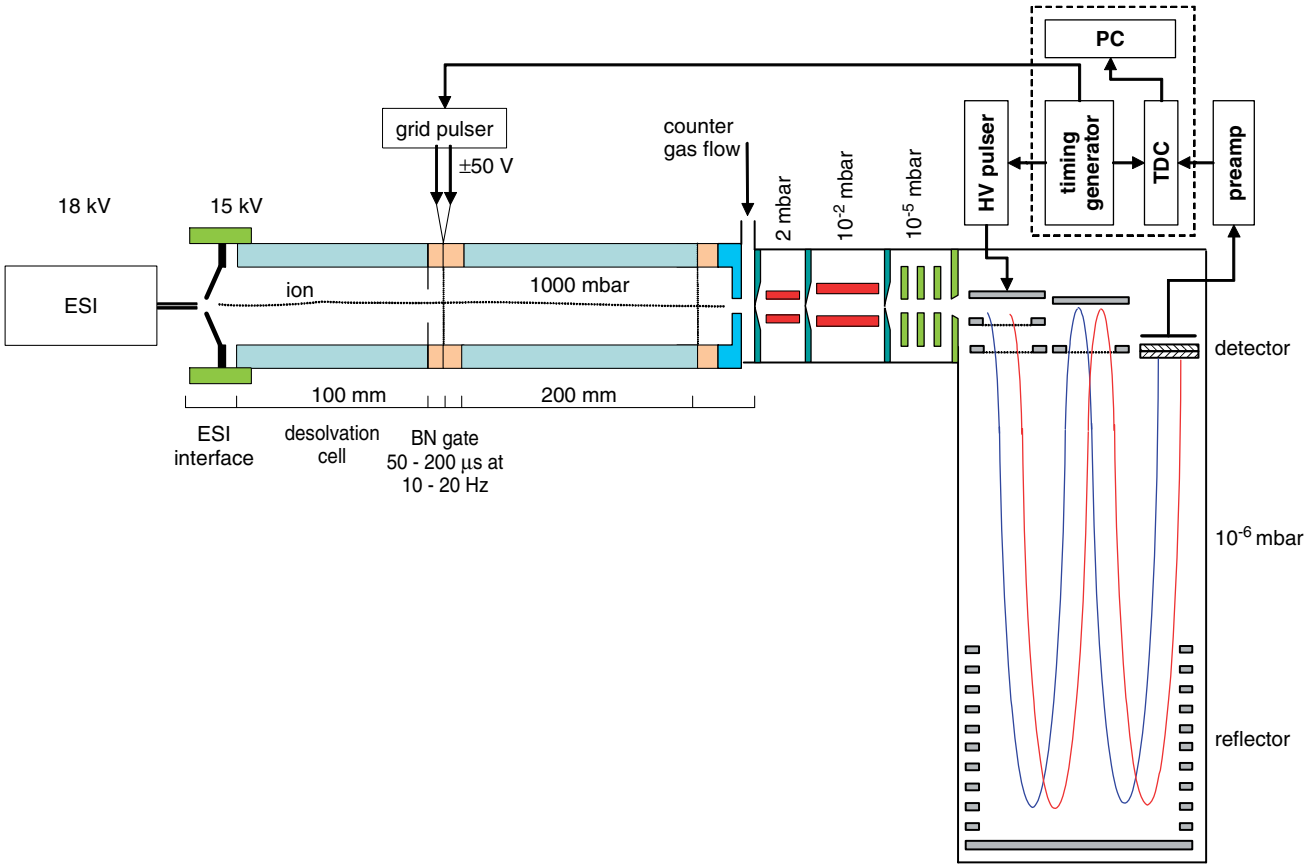

Figure 1. Schematic of an ambient-pressure IMS(tof)MS. Various components include (1) an electrospray ionization (ESI) source, (2) an ESI interface to the ion mobility spectrometer, (3) a desolvation chamber where the electrospray solvent is evaporated, (4) an ion gate which pulses packets of ions into the drift region, (5) the drift region where ions are separated according to their mobility, (6) a pinhole interface to vacuum, (7) transfer and focusing ion lenses to move the ions from high pressure to low pressure (8) a reflectron time-of-flight mass spectrometer. (Compliments of TofWerk, AG Thun, Switzerland).

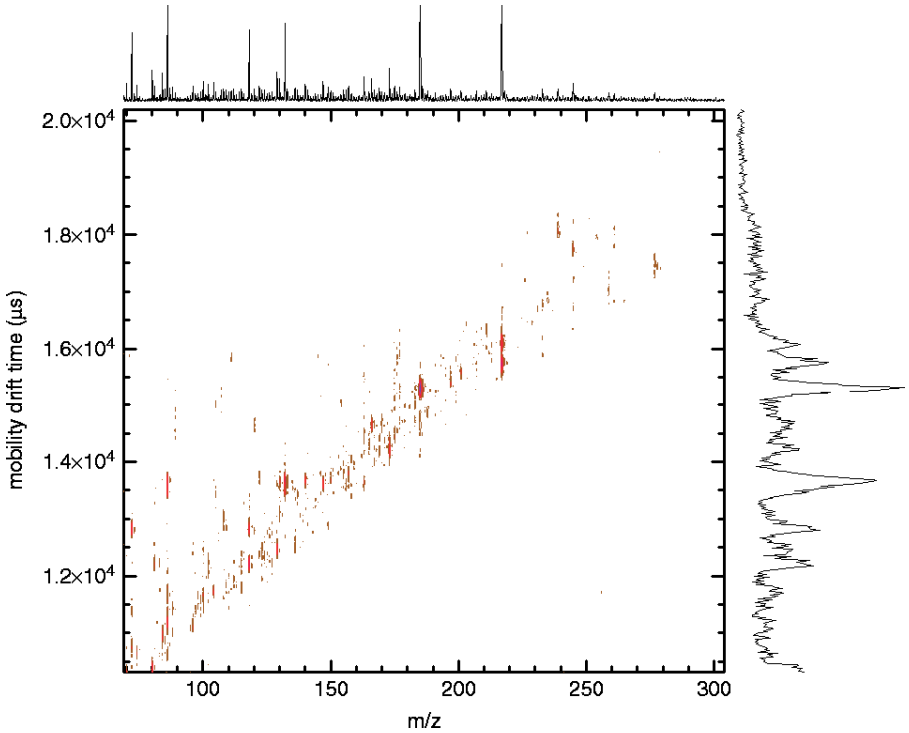

Figure 2. Two dimensional direct infusion ESI-IMMS spectrum of *E. Coli* culture producing over 1000 metabolite peaks. Reprinted from Dwivedi P, Wu P, Klopsch SJ, Puzon GJ, Xun L, Hill HH Jr. Metabolic profiling by ion mobility–mass spectrometry (IMMS). *Metabolomics* 2007, DOI: 10.1007/s11306-007-0093-z. Copyright (2007) with permission from Springer Science and Business Media.

the mobility space and that on the right margin is the ion mobility spectrum integrated across the mass space.

Figure 3 shows similar IMMS spectra for a mixture of peptides from a protein digest.[89] In this two-dimensional spectrum the presence of two 'trend lines' is clearly visible. The lower trend line passes through peaks for those peptides with only one charge while the upper trend line passes through the peaks produced from the doubly charged peptides. One of the practical advantages of using IMS for mass spectral analysis is this ability to separate multiple-charged ions generated from ESI.

Another principal advantage of IM(tof)MS is that fragmentation of a mobility-separated ion can lead to MS/MS analysis. A number of approaches for generating MS^2 spectra by IMMS have been developed. For example, voltages at the skimmer electrode in ambient-pressure interfaces can be increased to produce fragmentation of mobility-separated ions. Fragment-ion spectra for individual compounds in a mixture are separated in the 2D spectra by the drift times of the parent ion.[90] Surface induced dissociation (SID) can also be used to provide fragmentation patters of mobility separated ions.[91]

A second IMS can be incorporated prior to the IM(tof)MS to improve peak capacity.[92] Figure 4 shows the schematic of the IMS-IMS-TOFMS. The two dimensional separation is obtained by exiting the peptides in the region between the two ion mobility spectrometers such that the structure of the ions is changed from one spectrometer to the other.[53,93] By this two-dimensional approach, peak capacities in IMS can be enhanced by a factor of at least 10 and up to ~60 to 80. In addition, modulation of the field in a split-field IMS can provide for high-throughput multidimensional separations.[94]

The newest version of an IM(tof)MS, which is commercially available from Waters, is the traveling-wave ion mobility spectrometer described above. The commercial version is called the Synapt HDMS. A primary advantage of

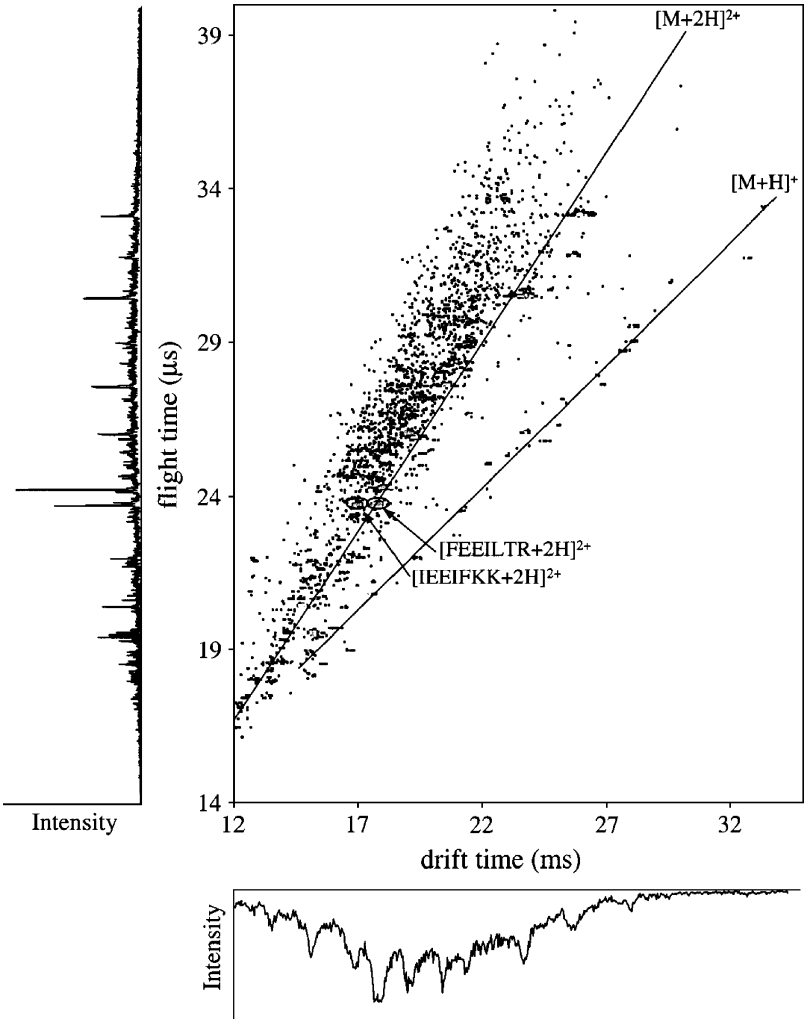

Figure 3. Contour plot of drift times and flight times for direct electrospray of peptide mixtures obtained from a tryptic digest for a creatine phosphokinase. The flight times relate to mass and the drift times relate to mobility. The lines drawn on the plot indicate the locations of the $[M + H]^+$ and $[M + 2H]^{2+}$ families. The mass spectrum at the left was obtained by summing all intensities at each flight time across the drift time distribution. The drift-time spectrum at the bottom was obtained by integrating across the flight region for each drift time. Reprinted from Kindy JM, Taraszka JA, Regnier FE, Clemmer DE. Quantifying peptides in isotopically labeled protease digests by ion mobility/time-of-flight mass spectrometry. *Analytical Chemistry* 2002; **74**: 950–958. Copyright (2002) American Chemical Society.

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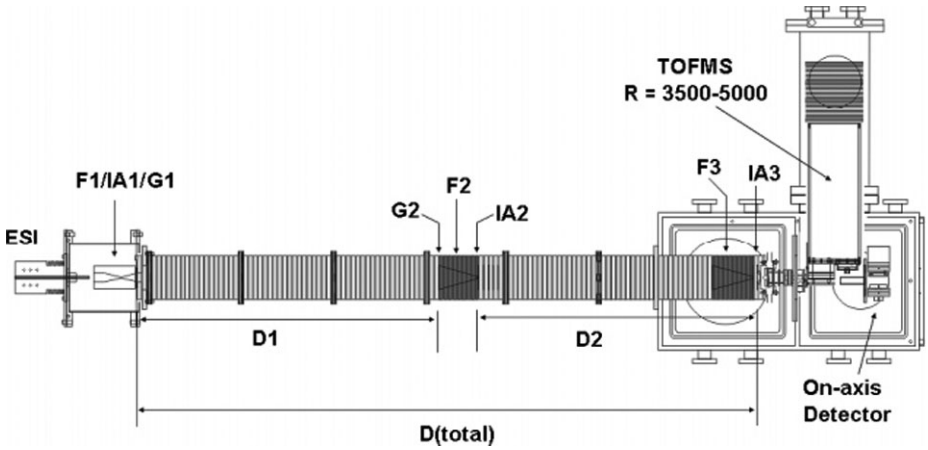

Figure 4. Schematic of an IMS-IMS-TOF Reprinted from Merenbloom SI, Bohrer BC, Koeniger SL, Clemmer DE. 'Assessing the peak capacity of IMS-IMS separations of tryptic peptide ions in He at 300K', *Analytical Chemistry* 2007; **79**: 515–522. Copyright (2007) American Chemical Society.

this combination is that the sensitivity of the mass spectrometer is not compromised by the duty cycle of the IMS as is common with other mobility-drift cells.[95] Figure 5 shows the schematic diagram of the Synapt HDMS. From left to right the components are as follows: The ionization source is an electrospray source which is orthogonal to the ion path. Once ionized and desolvated, the ions are guided into a quadrupole mass spectrometer which can be operated as a mass filter. Mass-selected ions are then trapped prior to the ion gate of the IMS. Periodically the ions are gated into the mobility cell and separated as a function of mobility. The ion swarm exiting the ion mobility cell is then focused into the time-of-flight mass spectrometer for a two-dimensional analysis. Although this first-generation mobility cell has limited resolving power, the addition of mass spectrometers on either side of the cell coupled with an ion concentration trap prior to the ion gate, provides a versatile and powerful analytical tool, especially since the mobility cell can also serve as a collision cell to provide Q-TOF like data. Figure 6 demonstrates the resolving power of the IMS with respect to a protein digest of peptides. Separation of singly charged peptides from multiple-charged peptides is easily observed.

An alternate ionization method for IM(tof)MS is matrix-assisted laser desorption ionization (MALDI).[96] This instrument uses a laser pulse instead of an ion-gate to generate a narrow packet of ions for IMS separation. One primary advantage to the pulsed source is that the entire ionized sample is used and thus sensitivity is potentially higher. Figure 7 shows a schematic of the MALDI-IMMS in which either a UV or an IR-laser can be used as the ion source.[97] In this configuration, the MALDI source is operated at reduced pressure as is the ion mobility cell. Because ions are created and separated at a reduced pressure the interface to the mass spectrometer is more efficient and the overall sensitivity is good compared to ambient pressure ESI-IMMS. Figure 8 shows a typical spectrum obtained from the MALDI-IMMS demonstrating separate trend lines for peptides and lipids. Thus, it is possible to separate classes of compounds along the mobility trend line. A particularly exciting recent development with MALDI-IMMS is the ability to image tissues for specific classes of compounds.[98]

Coupling DMS with a drift-time IM(tof)MS provides three-dimensional separations.[99] A schematic of a DMS-IMS-TOFMS design is illustrated in Fig. 9. The DMS is a cylindrical design with the interface to the low pressure section of the IMS-TOF on axis with the concentric DMS electrodes. A key element of importance in this ambient to vacuum interface is an ion funnel which traps and focuses ions, reducing ion losses in the interface. In addition, collisional heating at the DMS-IMS interface can be used to probe conformation of proteins.[100] With the combination of DMS and IMS it is possible to distinguish many more protein conformations than either DMS or IMS alone.

DMS, because it is based on the difference in mobilities of an ion in high fields, is more orthogonal to mass than drift-time IMS and thus when placed in front of an IMS-TOF provides a third degree of separation in which conformers and isomers can be separated prior to the IMS-TOF analytes. Figure 10 shows the comparison of the drift-time ion mobility with the DMS for several charge states of ubiquitin ions. Distinct conformers of the charge-state ions are identified in the boxes. Figure 11 provides an example of this 3D separation in which a complex mixture of peptides was separated in compensation voltage (CV), drift time, and flight-time space.

Ion mobility (quadrupole) mass spectrometry (IM(q)MS)

Ambient pressure IMS was first interfaced to a quadrupole mass spectrometer back in 1971 to obtain mass-selected ion mobility spectra.[82] Figure 12 shows a more recent but similar IM(q)MS design to that of the 1971 version.[101] The primary difference is that the ionization source is an electrospray source rather than a radioactive ^{63}Ni source and the mobility cell is a high-resolution cell. In theory the IM(q)MS can be scanned to obtain a 2D mass-mobility spectrum similar to that of an IM(tof)MS but the scan rate is much slower. Thus, IM(q)MS is more appropriate for targeted isomeric and isobaric separations in which the mass spectrometer is operated in the single ion monitoring mode.

There are now countless examples of isomer separation by IMS prior to MS. One recent example involved the

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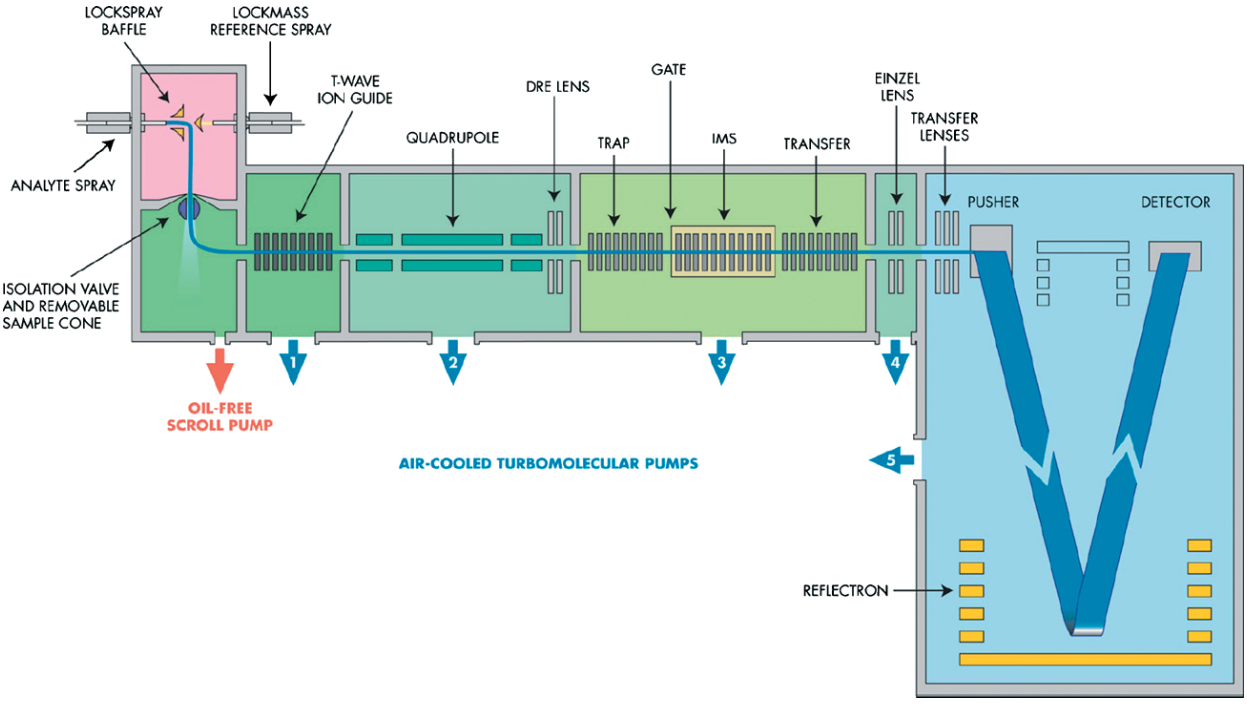

Figure 5. Synapt HDMS system reprinted from Pringle SD, Giles K, Wildgoose JL, Williams JP, Slade SE, Thalassinos K, Bateman RH, Bowers MT, Scrivens JH. An investigation of the mobility separation of some peptide and protein ions using a new hybrid quadrupole/traveling wave IMS/TOF instrument. *International Journal of Mass Spectrometry* 2007; **261:** 1–12. Copyright (2007) with permission from Elsevier.

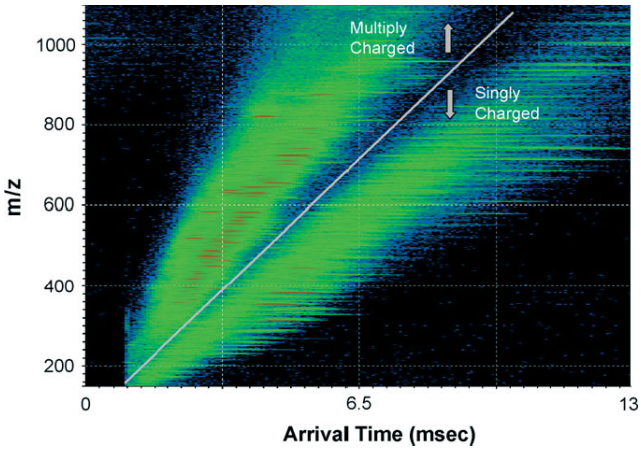

Figure 6. A 2D plot of ion-arrival time *versus m/z* for a protein digest mixture obtained using TWIMS. Reprinted from Pringle SD, Giles K, Wildgoose JL, Williams JP, Slade SE, Thalassinos K, Bateman RH, Bowers MT, Scrivens JH. An investigation of the mobility separation of some peptide and protein ions using a new hybrid quadrupole/traveling wave IMS/TOF instrument. *International Journal of Mass Spectrometry* 2007; **261:** 1–12. Copyright (2007) with permission from Elsevier.

addition of a chiral modifier to the drift gas as shown in Fig. 12.[15] The versatility of using different buffer gases or buffer gases modified by volatile compounds can affect the interaction of the ion with the buffer gas as it drifts through the mobility cell. The addition of modifiers and alternative drift gases are easier to accomplish with ambient pressure IMS but might also be possible with reduced pressure cells.

In this particular application, a chiral modifier is added to the nitrogen buffer gas at a mixing ratio of a few parts per million. For example, when 10 ppm of (S)-(+)-2-butanol was added to the buffer gas, enantiomers of atenolol were separated in the gas phase in a few milliseconds as shown in Fig. 13. To date, all enantiomers investigated in this manner have been separated by chiral IMS prior to mass spectrometry, making IM(q)MS a powerful method for chiral analyses. A commercial version of a chiral IM(q)MS is available from Excellims, Inc.

As stated earlier, one weakness of drift-tube IMS instruments is that the ion gate is only open for about 1% of the duty cycle. Thus when a continuous ionization source such as ESI is used, 99% of the sample is discarded. By using a time-dispersive approach the efficiency of the IMS can be improved to about 10%. Both Fourier transform[102] and Hadamard transform[103,104] as well as other multiplex methods have been reported.[105] Nevertheless, alternative methods in which sample ions are continuously introduced into the mobility spectrometer are still desirable.

Continuous introduction of a mobility-selected ion into a mass spectrometer is possible with a DMS. As described above, DMS separations are based on their mobility differences in both high and low-electric fields. Figure 14 shows an early design of a DMS interfaced to a quadrupole MS.[106] In the operation of this configuration, the CV spectra are obtained for specific mass to charge ratio or mass spectra are obtained at a specific CV. The primary advantage of DMS is its ability to separate cluster ions generated during the electrospray process from the analyte of interest, reducing chemical noise and increasing the signal-to-noise ratio. In later designs, the

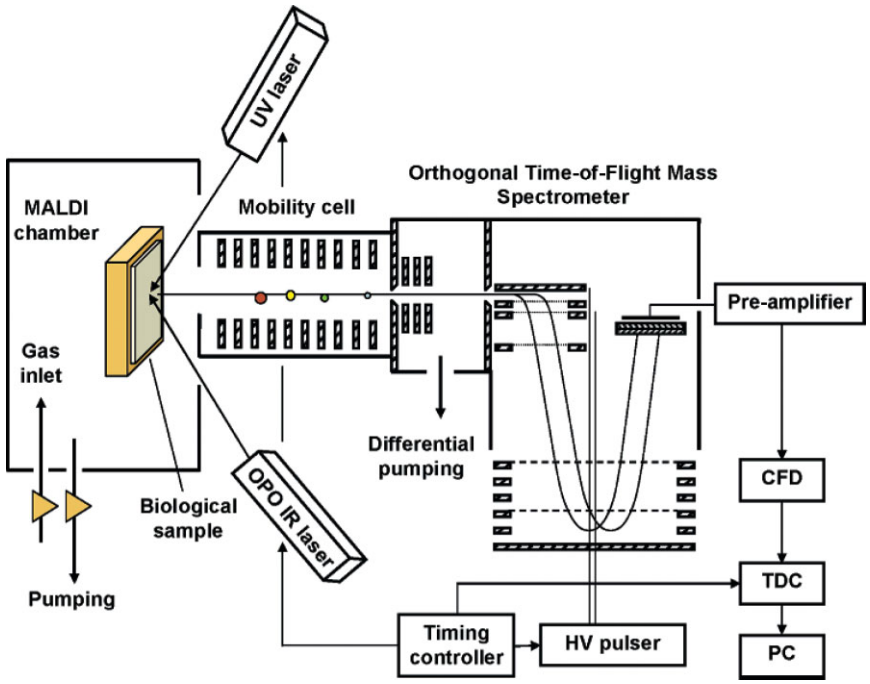

Figure 7. Schematic of IR and UV-MALDI-IM-oTOF-MS. Reprinted from Woods AS, Ugarov M, Jackson SN, *et al*. ''IR-MALDI-LDI combined with ion mobility orthogonal time-of-flight mass spectrometry''. *Journal of Proteome Research* 2006; **5**: 1484–1487. Copyright (2006) with permission from American Chemical Society.

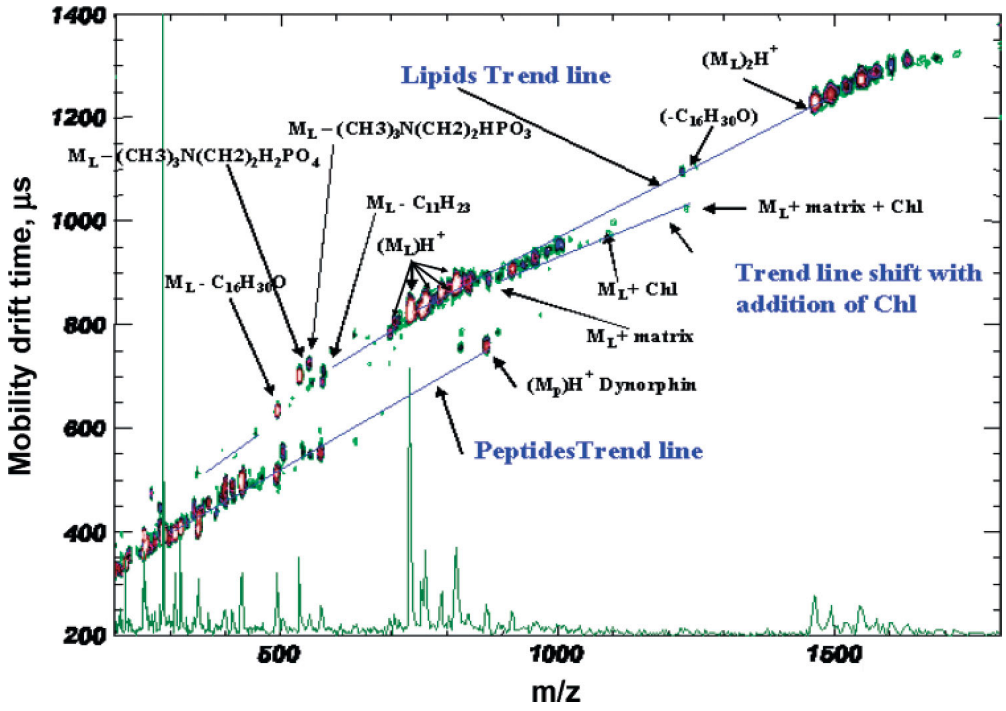

Figure 8. MALDI IM(tof)MS spectrum showing separate trend lines for peptides and lipids. Reprinted from Woods A, Ugarov M, Egan T, Koomen J, Gillig KJ, Fuhrer K, Gonin M, Schultz JA. Lipid/peptide/nucleotide separation with MALDI-ion mobility-TOF MS. *Analytical Chemistry* 2004; **76**: 2187–2195. Copyright (2004) American Chemical.

electrospray-DMS-MS combinations incorporated a curtain gas between the electrospray and the DMS to reduce solvent and water clusters from entering the high voltage region of the mobility spectrometer. When a single mass is monitored with the mass spectrometer, conformer separations are possible. Figure 15 demonstrates the use of DMS for the separation of gas-phase conformers of the +12 charge state of bovine ubiquitin. As the DV is increased, more of the protein conformers are separated. Similar results have been demonstrated for other charge states and other proteins.[107]

Continuous introduction of mobility-selected ions have also been investigated by interfacing an aspiration-type ion mobility spectrometer to a Sciex API-300 triple quadrupole mass spectrometer.[69] The purpose of these studies were to

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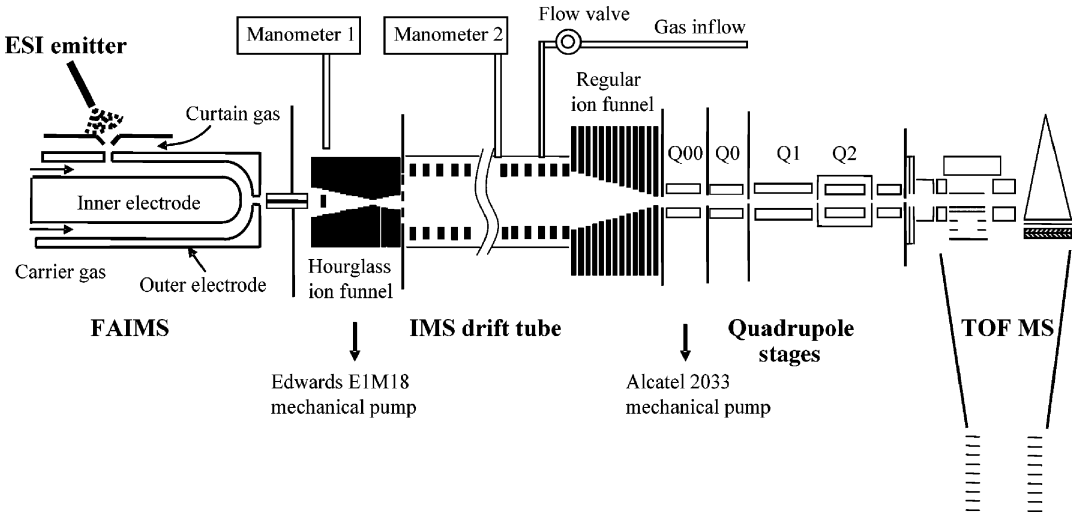

Figure 9. DMS-IMS-TOFMS design using an ion funnel as the interface between the ambient-pressure DMS and the reduced pressure IMS. Reprinted from Tang K, Li F, Shvartsburg AA, Strittmatter EF, Smith RD. Two-dimensional gas-phase separations coupled to mass spectrometry for analysis of complex mixtures. *Analytical Chemistry* 2005; **77**: 6381–6388. Copyright (2005) American Chemical Society.

investigate the separation mechanism of the aspiration-type ion mobility spectrometer using 2,6-di-*tert*-butyl pyridine and dimethyl methylphosphonate.

Ion mobility (ion trap) mass spectrometry [IM(it)MS]

A commercial version of the DMS-MS in which the DMS is interfaced to an ion trap or triple quadrupole mass spectrometer is available from Thermo Fisher Scientific, Inc. The Thermo Fisher technology is called FAIMS (high-field asymmetric waveform ion mobility spectrometry). In their configuration a novel FAIMS design is positioned between the electrospray and the mass spectrometer to reduce chemical noise and select analyte ions of interest after liquid-chromatographic separation and electrospray ionization. Figure 16, from a triple-quadrupole analysis, shows a mass-selected liquid chromatogram of norverapamil in human urine.[108] The figure on the left shows the isobaric chemical noise without the DMS while the figure on the right demonstrates the selectivity of the FAIMS when the CV and DV have been optimized for norverapamil. Signal-to-noise is increased significantly. Another advantage of FAIMS is the ability to separate multiple-charged compounds in the mobility space where one charge state does not interfere with the mass analysis of a targeted-charge state.

Drift-time IMS instruments have the advantage of high-resolution separation of isomers as a function of their collision cross-section. Before introduction into an ion trap (IT), a second-ion gate is required to select an ion of a specific mobility.[109] Figure 17 shows a schematic of a drift-time IMS interfaced to a quadrupole ion trap. Note the two Bradbury–Nielsen ion gates. The second gate is opened at a specified delay time after the first gate to select an ion of a specific mobility for injecting into the ion trap. This process is repeated until there is sufficient ion concentration in the trap to perform MS^n analysis on the mobility-selected ion. Figure 18 demonstrates the separation and mass spectra of mobility-selected ions.[103] Spectrum #1 illustrates the ion mobility separation of three isomers, hesperidin, neohesperidin, and rutin adducted with silver from a mixture. Spectrum #2 shows the overlaid ion mobility spectra of the respective standards. Through the use of single-mobility monitoring, the ions contained in the drift time windows (a), (b), and (c) were fragmented to produce the mass spectra shown in 1(a), 1(b), and 1(c), respectively. Shown in bold text in 1(a) and 1(b), the presence of the ions 409 and 411 may be used to confirm the presence of either hesperidin or neohesperidin. However, the IMS separation prior to mass analysis is necessary to conclusively distinguish between the three isomers.

The reverse geometry in which ion traps are positioned prior to ion mobility cells can be used to concentrate ions before injecting ion pulses into the IMS.[21] Figure 19 depicts an IT-IMS in which mass-selected ions are introduced into a drift-time ion mobility spectrometer operated at reduced pressure. Ions may be accumulated, mass-selected, extracted as a narrow packet, focused at the entrance to the IMS drift cell, and detected as a function of their arrival time with an electron-multiplier located after the IMS cell. In one unique study using this reverse geometry arrangement, mass-selected amine isomer ions of ethylmethylamine and n-propylamine could not be separated by IMS when they were in the protonated form but when complexed in the ion trap with vapors of a crown ether, their mobilities were significantly different.[58]

Ion mobility (Fourier Transform Ion-Cyclotron Resonance) mass spectrometry [IM(fticr)MS]

The use of ion mobility with Fourier transform ion-cyclotron resonance mass spectrometry is less developed than IMS combinations with quadrupole, time-of-flight and ion-trap mass spectrometers. Early concepts involved the introduction of an IMS inside the ICR cavity.[110] More traditionally, however, a two-gate IMS can be interfaced in a

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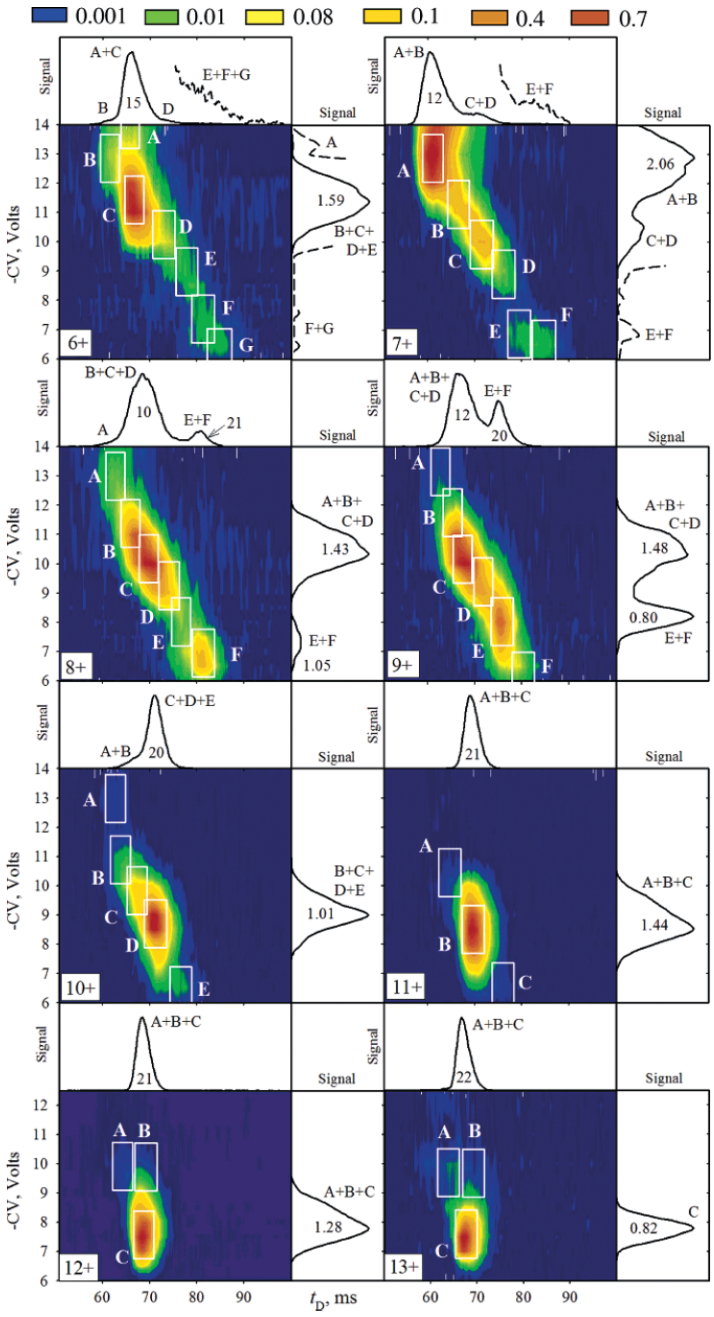

Figure 10. DMS/IMS palettes for ubiquitin ions with z = 6–13. To the right of each palette is the measured DMS CV spectrum (without IMS separation). On top of each palette is the composite IMS spectrum from the projection of palette on the drift-time axis. All plots (1D and 2D) are scaled to equal dominant peak intensity. In some IMS and DMS spectra, small features are magnified 25x (dashed lines). Boxes in palettes (described in the text) define distinct conformers marked in palettes, IMS, and DMS by letters. The apparent resolving power for features in IMS spectra and t_W (V) of features in DMS spectra are given. Reprinted from Shvartsburg AA, Li F, Tang K, Smith RD. Characterizing the structures and folding of free proteins using 2-D gas-phase separations: observation of multiple unfolded conformers. *Analytical Chemistry* 2006; **78**: 3304–3315. Copyright (2006) American Chemical Society.

manner similar to that shown in Fig. 17 in order to introduce mobility-selected ions into an FTICR for mass analysis.[111] In this study, isomeric phosphopeptides were separated by IMS and gated separately into the FTICR.

DMS is particularly useful for conformer recognition when interfaced to a high-resolution FTICR mass spectrometer.[112] Protein and organic polymer conformers as well as nominal masses of diprotonated and disodiated ions of polymers such as polyethylene glycols can be separated in DMS space prior to FTICR analysis.[113]

SELECTED IMMS APPLICATIONS

Applications of IMMS are more varied than IMMS designs and it would be impossible to review them all in this brief report. From fundamental studies of gas-phase ion structures to isomer separation in complex mixtures, IMS coupled with mass spectrometry offers a number of advantages over mass spectrometry alone. Some representative examples of IMMS analyses are given below to provide the reader with an appreciation of the breadth of applications that are possible.

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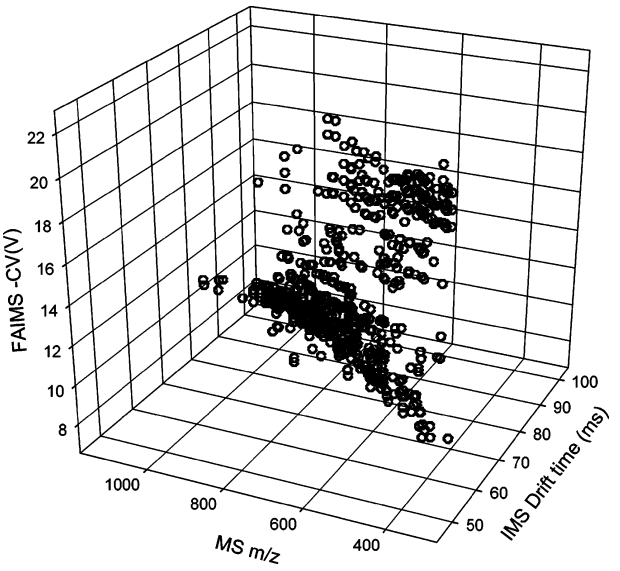

Figure 11. Complex peptide mixture separated in 3D space using DMS-IMS-TOFMS after direct infusion electrospray ionization. Reprinted from Tang K, Li F, Shvartsburg AA, Strittmatter EF, Smith RD. Two-dimensional gas-phase separations coupled to mass spectrometry for analysis of complex mixtures. *Analytical Chemistry* 2005; **77**: 6381–6388. Copyright (2005) American Chemical Society.

One of the primary reasons to couple ion mobility with mass spectrometry is for the investigation of gas-phase structures. IMMS has been applied to the determination of gas-phase structures of semiconductor materials important for understanding nanocrystalline materials as the size approaches interatomic distances.[114] Injected ion mobility was used to probe the geometries of gas phase ion clusters of germanium. Other ion clusters, such as those of silicon, along with their gas-phase transition states have also been evaluated with IMMS.[39] Transition metal-state selection[115] as well as the chemistry of carbon cluster can also be investigated by IMS.[116] Geometries of carbon cation clusters[117] and carbon anion clusters have been probed and related to fullerene and other structure formations. Direct analysis of fullerene contamination in nanotubes has been demonstrated as a specific application of IMMS.[118] IMMS of metallofullerenes has also aided in determining the position of the metal within the fullerene structure.[119]

While inorganic applications of IMMS are important, it is the extension of IMMS to measuring the size of biologically important molecules that has propelled IMS to a prominent position as an ancillary technique for mass spectrometry. Application of IMS analysis to saccharides, peptides, proteins, nucleic acids, drugs, and metabolites add a new dimension of information for the identification and characterization of these classes of biologically important compounds.

Application of IMMS to the analysis and characterization of carbohydrates is particularly promising because of the large number of isomers and the difficultly of distinguishing those isomers by MS alone. MALDI analysis produces sodiated ions from saccharides in which their structures become more similar than the neutral species.[120] These data suggest that the oxygen centers coordinate to the alkali ion and the saccharides wrap around the ion to produce a more dense structure than with protons. High-resolution IMS can separate many sodiated saccharides[121] and, by coordinating with ions such as cobalt acetate, many other saccharides can be separated.[122] DMS also adds selectivity for MS analysis of saccharides.[123]

Varying injection energies of a saccharide ion into an IMS or MS has produced unique product-ion MS spectra of isomers.[124] Mixtures of saccharides, however, complicate the interpretation of these spectra such that it is difficult to identify specific isomers with MS^n methodologies alone. Liquid chromatographic separation of sugars prior to IMS aid in identification[125] and high-resolution IMS prior to MS can resolve many oligosaccharides even without chromatographic separation.[122] The combination of IMS with MS analysis resolves many oligosaccharides and monosaccharides such that individual sugars from mixtures can be introduced into mass spectrometers so that the resulting MS^n spectra are not contaminated with isomer spectra. In addition to the identification of primary oligosaccharide structure, three-dimensional structure identification of glycans is possible with the aid of IMMS and molecular modeling.[126]

The need for high resolution and high-throughput methods for proteomics makes IMMS an ideal analytical tool for this application.[37] For the bottom-up approach, tryptic digests of proteins are either introduced after chromatography or directly infused into an IMMS.[127] More recently, desorption ESI has been used with tryptic peptides.[128] Data bases of collision cross-sections of peptides from tryptic digests are being developed to provide mobility signatures of the protein digests.[129] These signatures are aided by the separation of charge-state trend lines and peptide isomers.[130] LC-IMMS can be used for proteome profiling and for assessing the diversity of biological species.[131] Figure 20 provides a spectacular example of the 3D separation of a peptide digest of a plasma proteome.[132]

As demonstrated earlier, gas-phase IMS can be used to characterize the charge-state conformations of proteins.[133] A number of proteins and peptides have been investigated for the presence of unique gas-phase conformations: Equine cytochrome C,[134–136] ubiquitin,[100,113,137,138] bradykinin,[139] β-defensin,[140] and chicken-egg-white lysozyme[136] have been extensively examined by IMMS. In a remarkable application of IMMS, *Trp* RNA binding protein, TRAP, was found to produce protein rings in the absence of bulk water.[141] Ion mobility have also been used to investigate protein and peptide folding.[142] Effects of water on unfolding and refolding in the gas phase can be monitored with IMMS.[143] In addition, ion mobility can be used to determine the effect of d-residues on helix formation.[144]

Another class of biomolecules for which IMMS enhance current analytical methodologies is lipids. With the exception of water, lipids are the most common biomolecules found in the brain. Because lipids are less dense (not tightly folded) they produce a trend line separate from those of other potentially interfering biomolecules in tissue samples. Thus, direct profiling of the lipid distribution in brain tissue is

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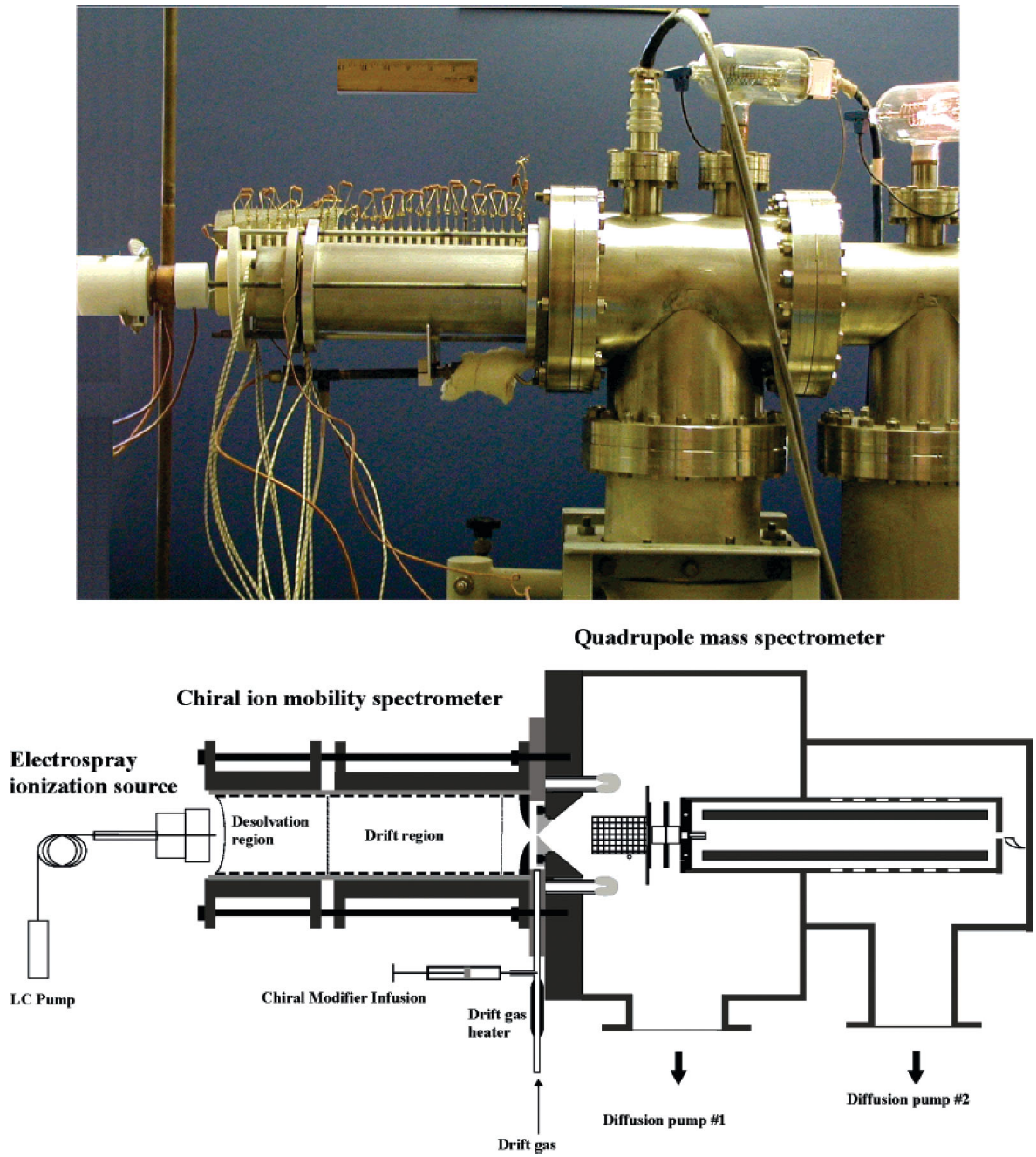

Figure 12. Photograph and schematic diagram of the electrospray ionization-ambient pressure ion mobility–mass spectrometer. The IMS cell was divided into a desolvation region (7.5 cm) and a drift region (25 cm) by a Bradbury–Nielsen ion gate, which was used to pulse ion packets into the drift region with a pulse width of 0.1ms. The Q-MS was operated in single-ion monitoring mode to monitor the arrival time distributions of mass-selected ions. Reprinted from Dwivedi P, Wu C, Matz LM, Clowers BH, Siems WF, Hill HH Jr. Gas-phase chiral separations by ion mobility spectrometry. *Analytical Chemistry* 2006; **78**: 8200–8206. Copyright (2006) American Chemical Society.

possible with MALDI-IMS-TOF.[145] Often drugs bind to lipids and the resulting change in ion density can be observed with IMMS.[146] A specific application of the analysis of biological samples for lipids using IMMS has been demonstrated for the determination of prostaglandins and thromboxane in lumbar spinal cord homogenate of guinea pig.[147]

IMMS can be used to separate oligonucleotide isomers or even different compositions of the same length.[148] Oligonucleotides fall on a unique and characteristic trend line.[149] Structural characterization of G-quadruplexes in deoxy-guanosine clusters can be determined by IMS in combination with mass spectrometry and molecular modeling.[150]

The separation of small molecules in complex mixtures is another area where IMMS offers advantages. Because there is a large number of small molecules under the molecular weight of 1000, many nominal isobaric compounds exist which require exact mass measurement

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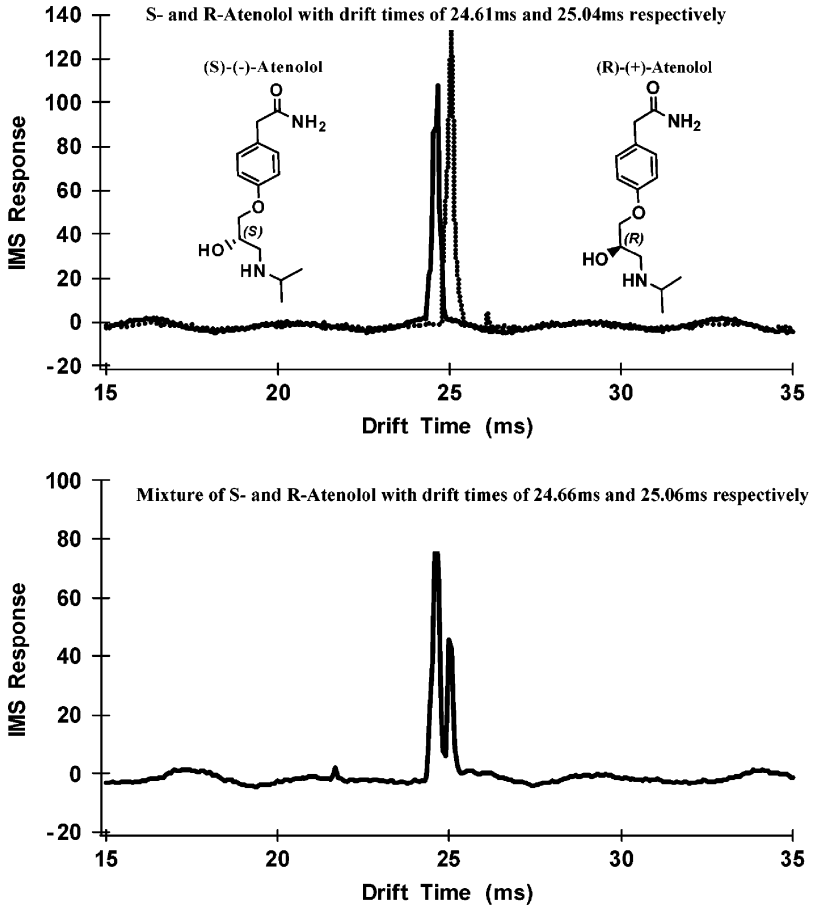

Figure 13. Gas-phase separation of atenolol enantiomers. The upper graph shows the superimposed spectrum of (S)- and (R)-atenolol obtained after introduction of 10 ppm (S)-(+)-2-butanol as the chiral modifier in the inert nitrogen drift gas. The bottom graph demonstrates the separation of the enantiomers from their racemic mixture. An average standard deviation of 0.05 ms in drift times was measured from three separation ion mobility measurements. Reprinted from Dwivedi P, Wu C, Matz LM, Clowers BH, Siems WF, Hill HH Jr. Gas-phase chiral separations by ion mobility spectrometry. *Analytical Chemistry* 2006; **78**: 8200–8206. Copyright (2006) American Chemical Society.

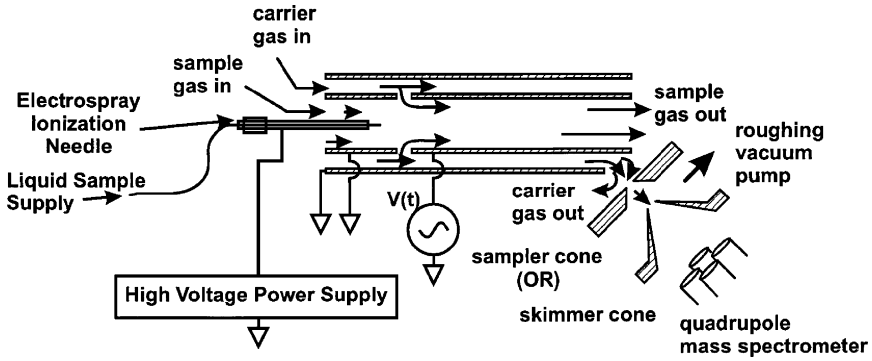

Figure 14. Schematic of an ESI-DMS instrument interfaced to a quadrupole mass spectrometer Reprinted from Guevremont R, Purves RW. High-field asymmetric-waveform ion mobility spectrometry–mass spectrometry: an investigation of leucine enkephalin ions produced by electrospray ionization. *Journal of the American Society for Mass Spectrometry* 1999; **10**: 492–501. Copyright (1999) with permission from Elsevier.

or chromatographic separations for their mass spectrometric analysis. The combination of ion mobility and mass spectrometry offers a rapid method for the analysis of small molecules in which many isobars are separated in mobility space before mass analysis.[151] All 20 common amino acids[152] as well as their phenylthiohydantoin derivitaves[153] can be separated rapidly by IMMS.[154] During the pharmaceutical analysis co-eluting metabolites can be separated by ion mobility to improve detection and quantification.[155]

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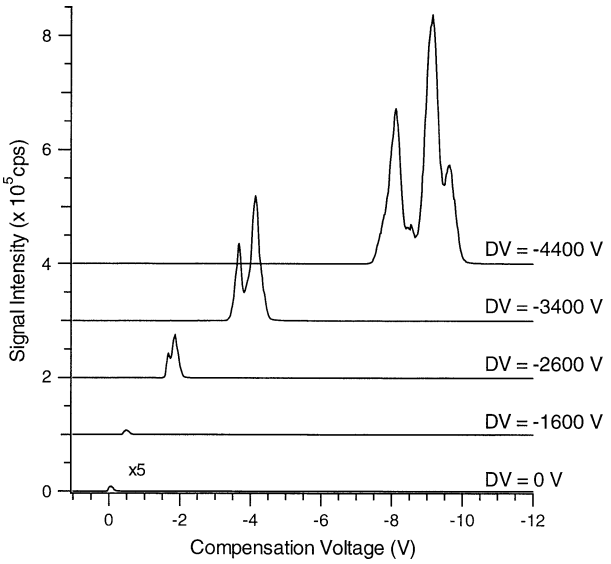

Figure 15. Ion-selective compensation voltage (IS-CV) spectra of the +12 charge state of bovine ubiquitin (*m/z* 714.8), collected at five dispersion voltages (DV). Reprinted from Purves RW, Barnett DA, Ells B, Guevremont R. Elongated conformers of charge states +11 to +15 of bovine ubiquitin studied using ESI-FAIMS-MS. *Journal of the American Society for Mass Spectrometry* 2001; **12**: 894–901. Copyright (2001) with permission from Elsevier.

The separation of chiral compounds in the gas phase can be accomplished by IMMS in one of two ways. In one approach, a chiral modifier can be added to the drift gas to create selective interactions with the enantiomers as they drift through the tube. Various enantiomers of drugs, amino acids, and sugars have been separated in this manner.[15] An alternative method includes the formation of diastereomer ions in the sample solution or during the ionization process.[156]

The detection of drugs,[90] explosives,[157] and chemical-warfare agents[24,158] by IMMS encounter fewer false positive responses due to chemical interferences than by either IMS or MS alone. Drugs can be detected directly in complex samples such as saliva with IMMS, offering a facile method for monitoring compliance.[149] Examples of IMMS in environmental applications have been few but IMMS methods are useful for the rapid analysis of aqueous samples as well as complex gaseous samples. For example, the analysis of drinking water for organic acids and other polar species can be conducted with IMMS at the sub-ppb level.[159] Nanomolar levels of perchlorate can be detected in water.[160]

In summary, the instrumental flexibility of coupling-ion mobility with mass measurements has lead to a wide variety of applications. From inorganic ion clusters to large biopolymers, from genomics to metabolomics, and from homeland security to environmental safety, isomer, and

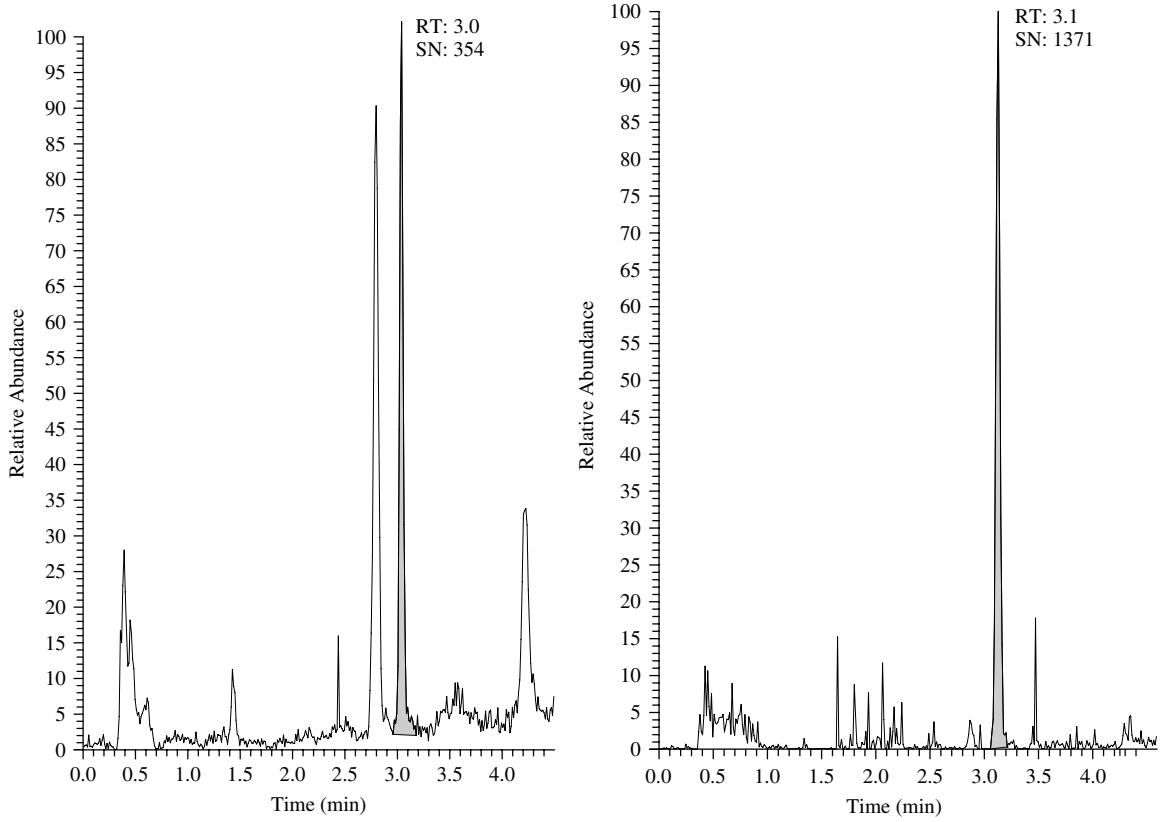

Figure 16. Mass selected liquid chromatogram of norverapamil in urine. The chromatogram on the left is without FAIMS selectivity and the one on the right shows significant improvement of signal-to-noise when FAIMS is selected for norverapamil. Shaded peak is that of norverapamil. (From Kapron J, Barnett DA. Thermo Electron Corporation Application Note: 362, 2006.) Copyright (2006) with permission from Thermo Fisher.

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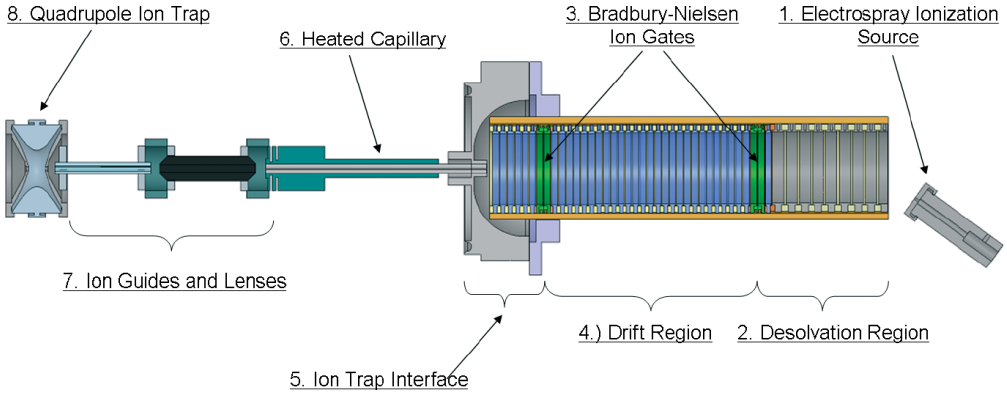

Figure 17. Schematic of the electrospray ionization, ambient pressure, dual-gate ion mobility, quadrupole ion-trap mass spectrometer. This instrument consisted of six primary units: an electrospray ionization source, an ion mobility spectrometer, a vacuum interface, ion guides and lenses, a quadrupole ion trap, and a PC-based data acquisition system (not shown). Reprinted from Clowers BH, Hill HH Jr. Mass analysis of mobility-selected ion populations using dual gate, ion mobility, quadrupole ion-trap mass spectrometry. *Analytical Chemistry* 2005; **77**: 5877–5885, Copyright (2005) American Chemical Society.

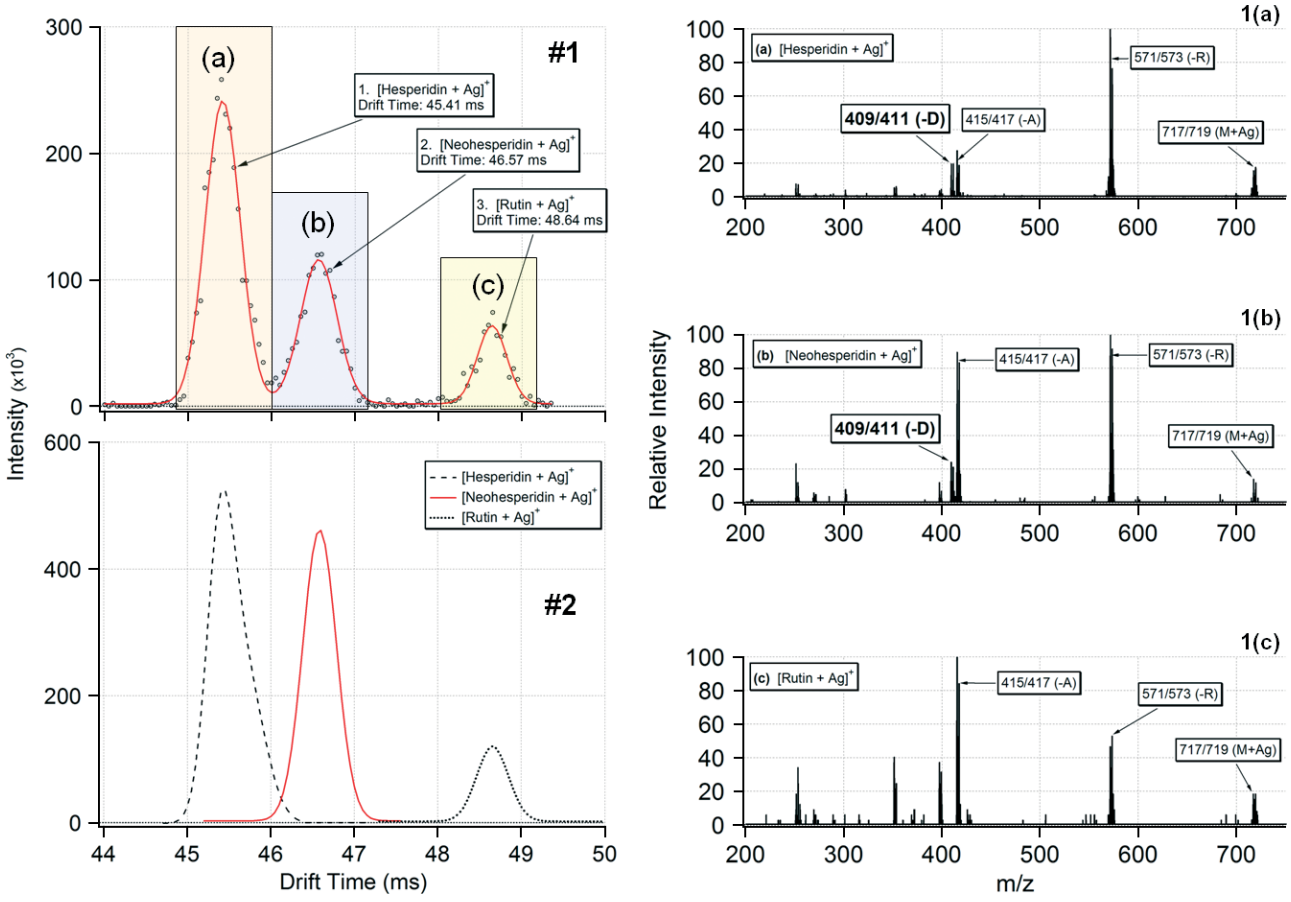

Figure 18. Drift-time ion mobility (ion trap) mass spectrometric data illustrating the necessity of isomer separation prior to MS analysis. Clowers BH, Hill HH Jr. Influence of cation adduction on the separation characteristics of flavonoid diglycosides isomers using dual-gate ion mobility-quadrupole ion trap mass spectrometry. *Journal of Mass Spectrometry* 2006; **41**: 339–351. Copyright (2006). Copyright John Wiley & Sons Limited. Reproduced with permission.

conformer differentiation by mobility measurements has significantly enhanced the power of mass spectrometry.

IMMS IN THE FUTURE

Given the ease with which mobility spectrometers can be interfaced to mass spectrometers and the value added to the data obtained, it would not be surprising to see the recent trend of combining ion mobility instruments with mass spectrometry instruments continue. Improvement in signal to noise enhancement, charge-state identification, structure classification, isomer separation, and conformer recognition offered by the addition of mobility to mass measurements creates a powerful analytical tool for both fundamental

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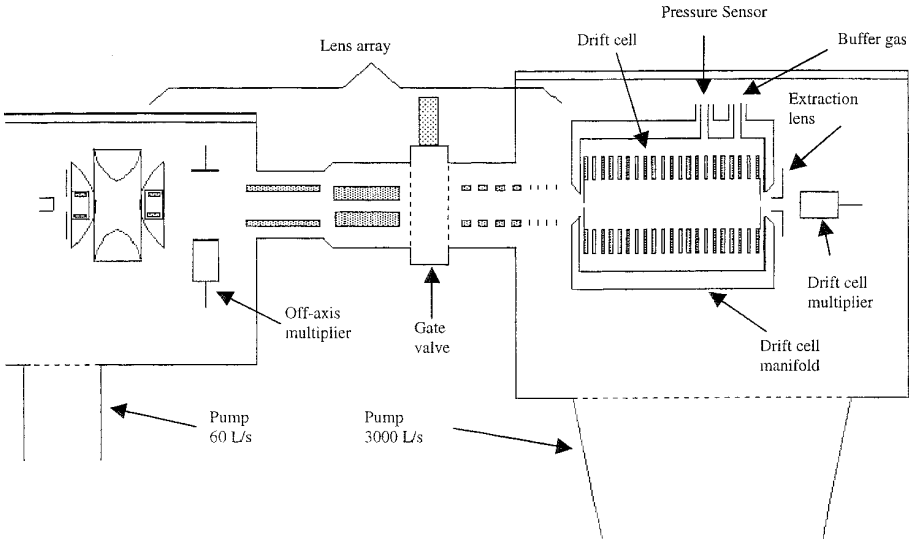

Figure 19. Schematic diagram of a tandem ion trap/ion mobility spectrometer. Reprinted from Creaser CS, Benyezzar M, Griffiths JR, Stygall JW. A tandem ion trap/ion mobility spectrometer. *Analytical Chemistry* 2000; **72**: 2724–2729. Copyright (2000) American Chemical Society.

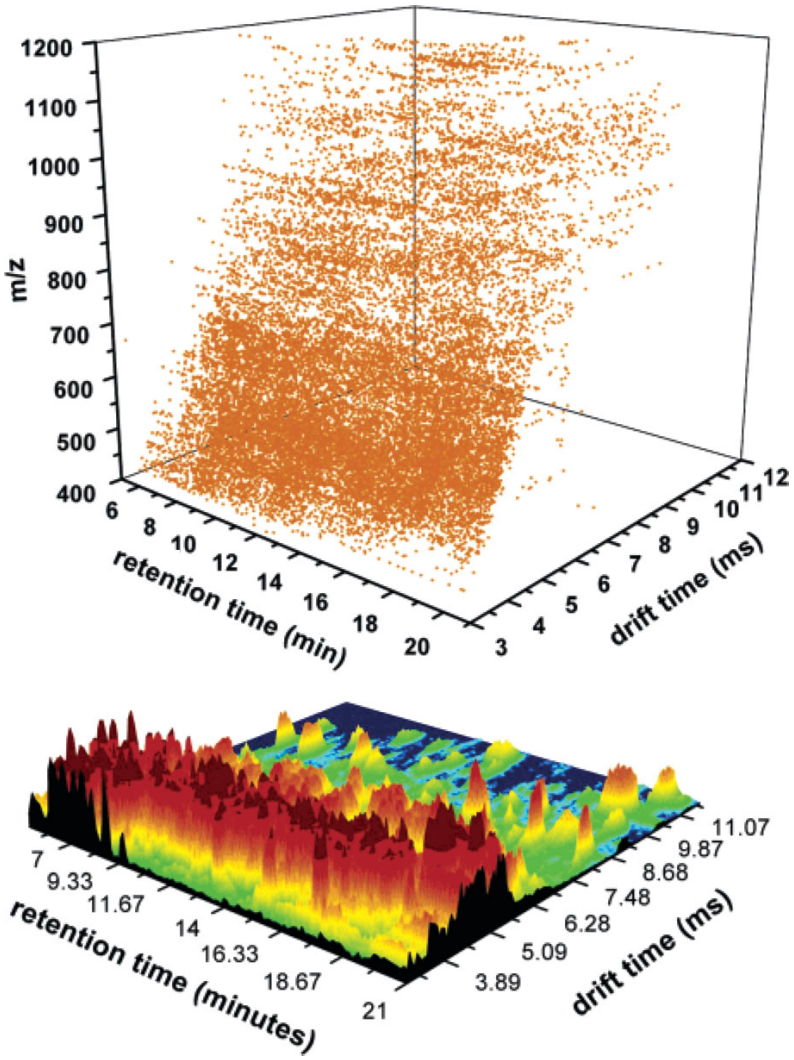

Figure 20. Three-dimensional peak positions obtained from the 6000 most intense features observed from the LC-IMS-TOF analysis of a plasma proteome. Reprinted from Valentine SJ, Plasencia MD, Liu X, Krishnan M, Naylor S, Udseth HR, Smith RD, Clemmer DE. Toward plasma proteome profiling with ion mobility-mass spectrometry. *Journal of Proteome Research* 2006; **5**: 2977–2984. Copyright (2006) American Chemical Society.

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investigations as well as a robust and practical method for the analysis of complex mixtures. Developments in higher-order differential ion mobility separations, multidimensional IMS, dense-phase IMS, novel interface technologies, and ionization sources may lead to improved sensitivity, quantification, resolving power and separation selectivity. As IMMS instruments become more commercially available and move from the research and development laboratory to the applications laboratory, the mobility advantage in mass analyses will continue to grow in importance. One might logically conclude that most mass spectrometers may someday be fitted with an ion mobility cell.

Acknowledgements

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