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Trapped ion mobility spectrometry: A short review

Mark E. Ridgeway[a], Markus Lubeck[b], Jan Jordens[c], Mattias Mann[d], Melvin A. Park[a,*]

[a] Bruker Daltonics Inc., MA, 01821, Billerica, United States
[b] Bruker Daltonik GmbH, Fahrenheitstr. 4, D-28359, Bremen, Germany
[c] DSM Resolve, Urmonderbaan 22, 6160 MD, Geleen, The Netherlands
[d] Proteomics and Signal Transduction, Max-Planck-Institute of Biochemistry, Am Klopferspitz 18, 82152, Martinsried, Germany

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ABSTRACT

Trapped ion mobility spectrometry (TIMS) hybridized with mass spectrometry (MS) is a relatively recent advance in the field of ion mobility mass spectrometry (IMMS). The basic idea behind TIMS is the reversal of the classic drift cell analyzer. Rather than driving ions through a stationary gas, as in a drift cell, TIMS holds the ions stationary in a moving column of gas. This has the immediate advantage that the physical dimension of the analyzer can be small (~5 cm) whereas the analytical column of gas – the column that flows past during the course of an analysis – can be large (as much as 10 m) and user defined. In the years since the first publication, TIMS has proven to be a highly versatile alternative to drift tube ion mobility achieving high resolving power (R ~ 300), duty cycle (100%), and efficiency (~80%). In addition to its basic performance specifications, the flexibility of TIMS allows it to be adapted to a variety of applications. This is highlighted particularly by the PASEF (parallel accumulation serial fragmentation) workflow, which adapts TIMS-MS to the shotgun proteomics application. In this brief review, the general operating principles, theory, and a number of TIMS-MS applications are summarized.

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1. Introduction

Ion mobility and mass spectrometry can be considered close relatives if not twins. Both can trace their lineage to research in the late 1890's when scientist first discovered that the application of electric and magnetic fields on charged particles generated from gas discharges could be used to separate charged species [1,2]. While mass spectrometry moved towards reduced pressures and developed rapidly, ion mobility remained a niche tool with limited interest [3]. In the 1960's McDaniel renewed interest in the technique by bringing ion mobility and mass spectrometry back together into hybrid instrumentation [4,5], and by the 1970's "plasma chromatography" brought IMS closer to the mainstream [6–8]. Still, during this time most efforts where focused in the development of stand alone IMS systems for military applications and the field once again went its separate way from mass spectrometry

* Corresponding author.
E-mail address: mel.park@bruker.com (M.A. Park).

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[9]. It was not until more recently with the development of sources operating at higher pressure, such as elevated pressure – matrix assisted laser desorption ionization (EP-MALDI), electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and atmospheric pressure photoionization (APPI) that IMS-MS systems began to be more commonly used for a range of applications including the detection of explosives and chemical warfare agents [10,11], characterization of polymers [12,13], cluster assembles [14–18] and biomolecular structure [19–31], as well as the analysis of complex mixtures [32–38].

The majority of ion mobility devices over the last 100 years have been of the dispersive type, namely a drift tube filled with an inert stationary buffer gas [39]. During analysis in such an instrument, the time which an ion, in the presence of a weak electric field, takes to traverse the length of the drift tube is measured. Knowing the length of the drift tube, L, and the drift time of the ion, one can calculate the steady state velocity of drift (v_d) of the ion. This velocity, v_d, is a linear function of the applied field, E, so long as E/N, where N is the number density of the gas, is small. The constant relating the two is termed the mobility, K, of the ion and is a measure of the drag force from the drift gas versus the driving force of the electric field, often described as related to the shape-to-charge ratio of an ion.

In order to achieve maximum resolving power in drift tube systems it's necessary to measure the ions' drift time as accurately as possible. It is therefore necessary to establish the start and stop of the ions' drift as accurately as possible. To this end, ions are gated into the drift tube with as narrow a time distribution as possible. As the resultant ion "swarm" drifts through the system diffusion and columbic forces lead to three dimensional broadening. The resolving power of the instrument is established as a balance between the work done on the ions (qEL), which tends to separate the ions according to mobility, versus the broadening of the ion packets via diffusion – which tends to cause the packets to spatially and temporally overlap.

In the case of hybridization with mass spectrometry (IMMS), the mass spectrometer acts as the detection system that establishes the 'stop' time for the ion drift – aka arrival time distribution (ATD). In such instruments, the interface between the mobility analyzer and mass spectrometer is critical. In early drift cell IMMS systems, this interface consisted of a simple conductance limit to allow ions to enter the MS system while maintaining the differential pumping needed to support the lower operating pressures required for mass analysis [4]. Until the 1990's these requirements severely restricted sensitivity in IMS systems when coupled with mass analyzers, as the vast majority of ions (>99%) would be either rejected at the entrance ion gate, or lost at the interface to the mass analyzer. The introduction of the RF confining ion traps and ion funnels in ion mobility systems [40–44] significantly improved the IMMS performance by allowing trapping and bunching of ions prior to injection into the IMS analyzer, as well as refocusing at the MS interface thus significantly improving sensitivity without loss in IMS performance.

Following the implementation of ion funnels into traditional drift tube analyzers, a second generation of ion mobility designs were developed using RF confinement not only before and after ion mobility, but also during the mobility analysis. RF confining drift tubes [21], traveling wave ion mobility [45], as well as a number of techniques where mobility is measured in RF multipoles and ion funnels have been described [46–48].

Building on this, in 2011 Park and coworkers introduced trapped ion mobility (TIMS) [49–51]. The basic idea behind TIMS is the reversal of the classic drift cell analyzer. Rather than driving ions through a stationary gas, as in a drift cell, TIMS holds the ions stationary in a moving column of gas. This has the immediate advantage that the physical dimension of the analyzer can be small – it only needs to be big enough to hold the ions stationary – whereas the analytical column of gas – the column that flows past during the course of an analysis – can be large and user defined. In the intervening years, TIMS has proven to be a highly versatile alternative to drift tube ion mobility in which ions are accumulated and analyzed within the ion funnel. The general operating principles [52], theory [53,54], and a number of applications [11,25,37,38] have recently been described in the literature as will be summarized below.

2. Theory

As mentioned above, an ion's mobility, K, is defined to be the steady state drift velocity, v_d, adopted by the ion in a given stationary gas under the influence of an electric field, E:

$$v_d = KE. \tag{1}$$

K is thus a function of the ion's interaction with the drift gas. This interaction is dependent on a large number of variables including, for example, the temperature, pressure, composition, and polarizability of the gas, and the charge, shape, and size of the ion. In order to simplify the description of mobility, a reduced mobility (K_0) maybe used which standardizes K to standard temperature, T_0, and pressure, P_0, conditions:

$$K_0 = K\frac{T_0}{T}\frac{P}{P_0}. \tag{2}$$

where T and P are temperature and pressure respectively. K_0 is a valuable piece of information, used to good effect in standalone IMS systems as a means of identification from libraries. When coupled to mass spectrometry K_0 becomes even more powerful as knowledge of both K_0 and mass-to-charge ratio (m/z) can indicate the chemical class of an ion, or can be used to calculate the collision cross section (CCS) of an ion through the Mason Schamp equation:

$$CCS = \frac{3ze}{16N}\frac{1}{K}\sqrt{\frac{2\pi}{\mu k_b T}} \tag{3}$$

where z is the charge on the ion, e is elemental charge, k_b, is Boltzman's constant, and μ is reduced mass. Substituting K_0 in for K in Eq. (3) eliminates the need for the number density term N:

$$CCS = \frac{3ze}{16}\frac{1}{K_0}\sqrt{\frac{2\pi}{\mu k_b T}}. \tag{4}$$

By grouping all the constants such as e, k_b, and the factor of 2π, we come to:

$$CCS = 18500\frac{z}{K_0}\sqrt{T\frac{Mm}{M+m}} \tag{5}$$

where only z, K_0, T, the mass of the ion, M, and the mass of the collision gas, m, are required to calculate a CCS. Like K0, CCS is a characteristic of the interaction between analyte ion and the drift gas. CCS is used to compare data obtained in the gas phase to structure measured using circular dichomism, nuclear magnetic resonances, x-ray crystallography [56], electron microscopy [57], as well as computationally calculated structures [19].

Conceptually, trapped ion mobility spectrometry (TIMS) represents the inversion of the conventional IMS experiment. That is, unlike drift tube IMS where ions are constantly pushed through a stationary gas by an electric field, TIMS uses an electric field to hold ions stationary against a moving gas. Importantly, however, the basic physical principles behind TIMS are the same as those in operation in drift cells – that is, pushing ions through a gas using an electric field. Because the fundamental physics of TIMS is the same as that in drift cells, the same basic concepts discussed above relating to the determination of K, K_0, and CCS still apply.