



Review article

Hybrid ion mobility and mass spectrometry as a separation tool



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ABSTRACT

Ion mobility spectrometry (IMS) coupled to mass spectrometry (MS) has seen spectacular growth over the last two decades. Increasing IMS sensitivity and capacity with improvements in MS instrumentation have driven this growth. As a result, a diverse new set of techniques for separating ions by their mobility have arisen, each with characteristics that make them favorable for some experiments and some mass spectrometers. Ion mobility techniques can be broken down into dispersive and selective techniques based upon whether they pass through all mobilities for later analysis by mass spectrometry or select ions by mobility or a related characteristic. How ion mobility techniques fit within a more complicated separation including mass spectrometry and other techniques such as liquid chromatography is of fundamental interest to separations scientists. In this review we explore the multitude of ion mobility techniques hybridized to different mass spectrometers, detailing current challenges and opportunities for each ion mobility technique and for what experiments one technique might be chosen over another. The underlying principles of ion mobility separations, including: considerations regarding separation capabilities, ion transmission, signal intensity and sensitivity, and the impact that the separation has upon the ion structure (i.e., the possibility of configurational changes due to ion heating) are discussed.

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1. Introduction

Ion mobility spectrometry (IMS), also at times known as plasma chromatography [1] and ion chromatography [2–4], was originally developed as a tool for the separation of ions of interest by a linear field applied to a drift tube containing a buffer gas [5]. The buffer gas impedes ion progress, counteracting the acceleration of the ions in applied electric fields. As a result, ions travel at a terminal velocity proportional to the inverse of their collision cross section (CCS), a parameter that describes the orientational average of collision rate, in a manner analogous to the terminal velocity of a skydiver depending on the skydiver's shape. The CCS is smaller for more compact (more spherical) molecules than for more extended ones (e.g., planar structures, extended chains, helices, etc.) and thus yields insight into the overall shape. For example, this insight has been used to determine that carbon clusters exist as chains, rings, planar graphite-like sheets, and fullerenes depending on the number of atoms in the clusters [2,6–11]. In the seemingly distant field of structural biology, the approach has been used to determine the topology of an intact ATPase as well as conditions that favor the attachment and detachment of different components and the dynamics of those components [12,13].

In addition to identifying the shape of a given ion, ion mobility can be used to separate mixtures containing isobaric (and thus isomeric) ions by shape [14]. In particular, the separation time of drift tube ion mobility spectrometry (typically milliseconds) fits well between that of liquid separation techniques such as liquid chromatography and capillary electrophoresis, with typical separation times of seconds to minutes, and mass spectrometry (MS), which often operates on the microsecond time scale. Because of the unique separation phenomenon, the ability to glean structural insights from the CCS, and the relative time scale of drift tube separations and mass spectrometric analyses, coupling IMS with MS can be used to influence a range of useful separation parameters, yielding: enhanced peak capacity, reduction in total analysis time, reduction of chemical noise, decreased detection limit, and valuable analyte structural information.

Since the dawn of the millennium, IMS has emerged as a powerful means of enhancing the separation of components found in complex mixtures – that is, these methods are especially valuable when coupled to other separation techniques such as mass spectrometry and liquid chromatography [15–26]. The extra dimension of separation has enhanced the number of peptides identified in proteomics studies [18,27–29] and enabled metabolomics studies [26,30,31]. The ability to dissociate ions in parallel [32–38] has promised to advance the identification of proteins in the field of proteomics [21,23,27,39]. The ability to distinguish isomers of glycans presents a novel diagnostic tool for disease progression [40–42]. And the ability to predict CCS from peptide sequence can enhance the confidence in peptide assignment [43–45]. Many other fields have benefited from the increased separation powers available when ion mobility spectrometry is coupled to mass spectrometry including petroleomics [46,47] and polymer separation [48–51].

One of the most powerful aspects of this technology is that it can provide information about the three-dimensional structures of ions – where few options for determining structure exist. While the determination of cross-section from the conformation of the molecule and the relation to diffusion constants was first described by Mack in 1925 using beeswax [52], it was not regularly applied to IMS for quite some time. This aspect of these measurements was revolutionized in the early 1990s by the Bowers and Jarrold groups when they compared measured mobilities or cross sections with values that were calculated for trial geometries generated by computations [2–4,6,53–58]. While this modern use of the approach is now widely used, from its inception, IMS was used to infer the

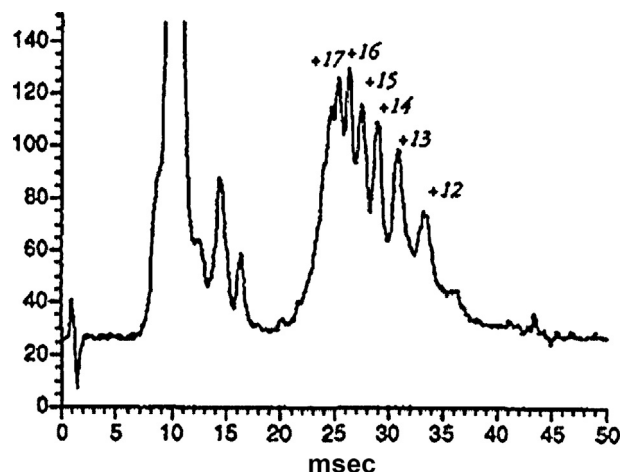


Fig. 1. ESI-IMS spectrum of cytochrome c showing separation of different charge states by IMS.

Adapted with permission from D. Wittmer, B.K. Luckenbill, H.H. Hill, Y.H. Chen, Electrospray-ionization ion mobility spectrometry, *Anal. Chem.*, 66 (1994) 2348–2355. Copyright 1994 American Chemical Society [59].

structure and composition of analytes, such as in the separation of the charge states of cytochrome c shown in Fig. 1 [59].

Groups at Bell Labs [60–62] and Georgia Tech [63,64] first coupled ion mobility spectrometry with mass spectrometry over 50 years ago but the technique saw limited analytical use. Much of the earliest instrumentation in this field was dependent upon scanning a dual gate ion mobility setup [60,62–64] to determine the mobility of ions by only gating out those ions that traversed the drift tube in a predetermined time, and then scanning the delay between the entrance and exit gates. IMS coupled to orthogonal time-of-flight (TOF) MS was first developed by McAfee et al. [60]; on a similar instrument Young et al. [61] was able to generate multiple pulses into the TOFMS flight tube per drift spectrum but still required scanning the pulses into the TOFMS flight tube to obtain a full spectrum [61]. Full spectral coverage, and the accompanying increase in throughput, was only obtained with the development of nested orthogonal TOFMS [65], whereby ions were pulsed into a TOFMS across the entire time course of the drift separation in order to obtain the mass and mobility for (conceptually) all ions in a single mobility separation as described in more detail below. The dramatic increase in throughput and sensitivity make this a key step delineating older techniques used for analyzing simple mixtures from newer experiments wherein complex mixtures can be analyzed. Demonstrations of high signal [18] with the new advances in instrumentation drove further advances in instrumentation as the requirements of different applications determined what aspects of the separation were preferable.

In this review we examine a range of IMS–MS-based experiments – primarily focused on enhancing separations of complex mixtures. Taking into account the wide range of needs of different experiments, we consider what factors might lead a user to prefer some techniques available for coupled mobility and mass separations. To better understand the distinctions between techniques, we will examine each technique individually, focusing on fundamentals of the technique, the separation capacity, the limits of detection, the relationship between the instrumentally measured mobility and the gas-phase structure, and the causes and effects of heating of ions within the instruments provided. For each technique we also provide an example experimental dataset and a very brief discussion of the data that is intended to familiarize the reader with how data from hybrid IMS–MS instruments is typically displayed. For a detailed understanding of each dataset that is shown, the interested reader will need to examine the original publication.

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