1. BACKGROUND AND SIGNIFICANCE

1.1. Ion Mobility Spectrometry in national security, industry, and human health

Small hand-held or bench-top instruments based on ion mobility spectrometry (IMS) operating at ambient pressure are today central to military preparedness and commercial aviation security as analyzers of trace levels of chemical agents or explosives.[1] No other instrument method has been used in life-critical venues in such large numbers with more than 60,000 hand-held IMS instruments in military establishments and ~20,000 explosives detectors in airports, and other sensitive locations, world-wide. Derivatives of these designs are now entering clinical practices,[2,3] have been used in industry for materials testing or environmental emissions[4,5] and are being considered for quality control/production of foodstuffs.[6,7]

The principles that control performance in these measurements are: a) gas phase chemistry where a substance is ionized through low energy ion-molecule reactions, photo-ionization, or electospray ionization and b) ion mobility where swarms of ions are separated or characterized for motion in an electric field through a supporting gas atmosphere. Selectivity in ion chemistry and competitive charge exchange can be complications in IMS applications; however, these are satisfactorily controlled with reagent gas chemistry in current methods and by pre-separations in emerging applications. In contrast, all small embodiments of IMS analyzers exhibit low resolving power significantly compromising specificity, hence confidence, of measurements.[8]

1.2. Resolving power in drift tubes IMS analyzers

In conventional designs in use widely for IMS, resolving power is governed by ion transport through wire-based ion shutters.[9-11] Injection pulse widths of 100 µs with final peak widths of 400 µs on drift times of 5 ms are not uncommon and lead to resolving powers of 20; often values are as low as 15. A consequence of low resolving power is lessened confidence of a measurement. Reductions in widths of the "wires", permitting injections below 50 µs, was demonstrated while unpromising practically.[12] Other barriers include the speed of ion swarms at ambient pressure and distortions of effective fields in the vicinity of the shutter.[10,11] In differential mobility spectrometry (DMS),[13,14] wire grids are eliminated and peak width is established by the gap or distance between plates. Resolving power for DMS instruments has been limited by inability to focus ions precisely in a uni-polar condition at ambient pressure. Improvements through reduced "effective" aperture widths are offset by losses in ion intensity.

A consequence of these physical barriers in ion swarm motion is a cap of 15 to 20 in resolving power for small instruments. This contrasts with values as large as 150 with large instruments[15] or comparable values when mobility measurements are made in non-clustering atmospheres of helium at 1 to 10 torr.[16,17] In practical analytical IMS, there has been no demonstration or suggestion of overcoming barriers on pulse width by improving ion injection methods. This limitation in resolving power has motivated the concept of tandem mobility instruments.

1.3. Emergence of tandem IMS analyzers

Since ambient pressure instruments in IMS and DMS are comparatively small and inexpensive, tandem configurations have been explored to aid specificity, dating first to the mid-1980s with a four stage drift tube of conventional design with linear or line of sight geometry. Three drift regions and an ion source volume were separated by three ion shutters.[18,19] Ions formed in the source region were injected using a first ion shutter into a drift region where ions swarms were separated in drift time. At the end of this first drift region, a second ion shutter was located and synchronized to the first shutter and control of delay could allow ions from only a portion of drift time to be isolated and passed to a second drift region. In this next drift region, vapors could be added to promote selective reactions or ions could be photo-fragmented and then characterized using a third drift region, also preceded with an

ion shutter. The concept was not developed owing to poor drift tube technology and improper control of gas flows. A successful tandem IMS for kinetic studies of decomposition of gas ions in air at ambient pressure was described in1996[20] and refined recently.[21-23]

In another tandem mobility analyzer, a micro-fabricated DMS analyzer (15 mm long) was combined with two miniaturized IMS detectors (10 mm long) providing two dimensions for ion characterization with K versus ΔK.[24,25] Ions were filtered in the DMS at specific compensation voltages and drawn into IMS drift tubes of appropriate polarity for a DMS/IMS measurement on each ion. The anticipated benefit of orthogonal characterization of an ion was not meritorious though resolution was leveled over a range of ion masses. A tandem DMS/IMS design was inverted for IMS/DMS[26] although the scanning speed of a DMS (0.5 to 2 Hz) is a poor direct match with the repetition rate of an IMS drift tube (10 to 30 Hz). Nonetheless, one peak for tyrosine-tryptophan-glycine in the IMS was resolved in the DMS into two conformer peaks. Apart from this success, ion motion in DMS/IMS and IMS/DMS was based only on physics of swarm mobility. Ion separations in tandem instruments at ambient pressure based only on principles of ion mobility in purified gas atmospheres should be considered a failed concept even though slightly different principles of mobility were employed. (This conclusion is significantly different from studies in non-clustering atmospheres where an an IMS/IMS instrument at 3 torr in helium atmosphere of helium in combination with a mass spectrometer showed an increase in separating efficiency of 8X with two-dimensional IMS for mixtures of tryptic peptides. The drift tubes were 100 cm long.[27])

1.4. Ion modification by chemistry in IMS: A basis for orgogonality in tandem methods

A distinct advantage of mobility measurements at ambient pressure is the capability to add reagent gases (or modifiers or shift reagents) into the drift gas to alter ion compositions, thus mobility coefficients, and ion peak separations. In the determination of F^-, the peak for O_2^- the reactant ion was displaced from the fluoride peak by addition of methylsalicylate in the gas atmosphere. The adduct ion between reagent and O_2^- provided airborne vapor monitoring of HF in ambient air by baseline separation with the fluoride peak.[28] Separation of ion peaks for ammonia, hydrazine, methylhydrazine and dimethylhydrazine is possible at ambient temperature when nonanone is added at 1 ppm into the drift gas.[29] Cluster ions form with ketone adducts on each of the available nitrogen bonded hydrogen atoms increased mass and cross-section to the core ion causing shifts in the drift times so that clustered hydrazine had the longest drift time and dimethylhydrazine the shortest.[30] Ions of pharmaceuticals were modified using polyethylene glycol (PEG) as a shift reagent with separation from matrix interferences by mobility[31] In the mobility separation of optically active aminoacids, an asymmetric volatile chiral reagent (in this instance (S)-(+)-2- butanol)permitted enantiomeric separations of atenolol, serine, methionine, threonine, methyl r-glucopyranoside, glucose, penicillamine, valinol, phenylalanine, and tryptophan from their respective racemic mixtures.[32]

In DMS measurements, modification of the supporting gas atmosphere to control analytical space in the mobility spectrum was first demonstrated with resolution of ion peaks of explosives[33] and is now a standard practice and commercialized.[34] The uniqueness of interactions that occur between an ion and reagent gas forms a basis for chemical orthogonality.

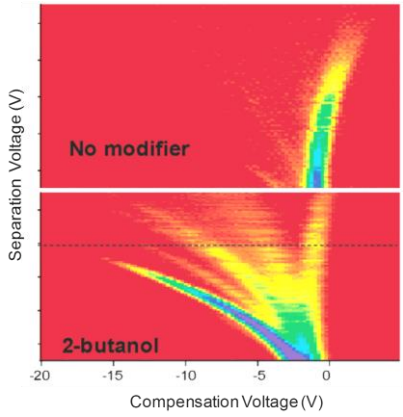

Figure 1. Effect of reagent gas (chemical modifier) on dispersion plot in DMS measurement of peptide.

The incorporation of an ESI source with DMS for measurements of biomolecules, here peptides, was first reported in 2006 with a DMS/MS instrument.[35] In a purified gas atmosphere, mobility separation of ion peaks for peptides was poor (Fig. 1) and attributed to the formation of higher order peptide aggregate ions (ion complexes) from the ESI source. This was changed with the addition of a reagent, butanol, which increased the selectivity of the separation by forming ion adducts of unique structure and differential mobilities. Still, the concept of chemical orthogonality was not explicitly described or exploited and all measurements were one-dimensional separations.

1.5. Selection of mobility configuration best to introduce orthogonality

A tandem confirmation of mobility instruments which provides a platform for demonstration of improved specificity of measurements by chemical orthogonality is a tandem DMS. A DMS is the mobility equivalent of an ion filter and thus, DMS/DMS is most attractive platform for these reasons

a. Ion isolation in mobility region. In DMS, an ion peak can be continuously filtered or isolated and passed into the next mobility region which can be scanned or set to a pre-selected mobility value.

b. Timing and scanning. A complete tandem measurement can be made where the third region is rapidly scanned while the first region is swept providing a two dimensional characterization of ions as ion intensity, compensation voltage DMS1, and compensation voltage DMS2. This is true DMSxDMS.

c. A last reason is practical which is the facile introduction of reagents into the relatively low gas volume of a DMS and the multiple effects including changing alpha functions that exist with ion motion in DMS.

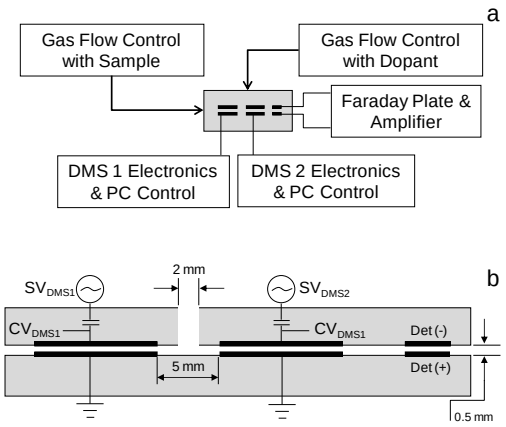

Figure 2. Schematics of (a) DMS/DMS system with (b) enlarge graphic of DMS/DMS analyzer with two stages: DMS1 and DMS2.

1.6. Research goals

Our research plan involves experiments:

1) to clarify the design requirements and operation of a DMS/DMS instrument to best implement and test the concept of chemical orthogonality;
2) to apply insights from these experiments to construct a second generation DMS/DMS instrument; and
3) to investigate the impact of reagent structure and ion-reagent association on orthogonality, that is in-filling the area of compensation voltage plots of DMS 1 versus DMS2.
4) to establish ion fragmentation and determine quantitatively field thresholds for ions in purified air and in reagent rich atmospheres.

Specifically, we intend to determine the range and extent of chemical structures and the experimental conditions needed to create chemical orthogonality in mobility methods, specifically a DMS/DMS instrument. In addition to the fundamental interests associated with ion-reagent interactions and ion fragmentation at ambient pressure, the results from these investigations are expected to inform decisions and design elements for a next generation of mobility spectrometer for national security, clinical applications, and industry uses.