

Ion Trapping for Ion Mobility Spectrometry Measurements in a Cyclical Drift Tube

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ABSTRACT: A new ion trapping technique, involving the accumulation of ions in a cyclical drift tube, as a means of enhancing ion signals for scanning ion cyclotron mobility measurements has been modeled by computational simulations and demonstrated experimentally. In this approach, multiple packets of ions are periodically released from a source region into the on ramp region of the cyclical drift tube and these pulses are accumulated prior to initiation of the mobility measurements. Using this ion trapping approach, it was possible to examine ions that traversed between 1.83 and 182.86 m (from 1 to 100 cycles). Overall, we observe that instrumental resolving power improves with increasing cycle numbers; at 100 cycles, a resolving power in



excess of 1000 can be achieved. The utility of this method as a means of distinguishing between analytes is demonstrated by examining the well-characterized model peptides substance P, angiotensin II, and bradykinin.

I on mobility spectrometry (IMS) is a well-established analytical method that can be used to separate species based on differences in their mobilities through buffer gases.¹⁻³ Although there is an extensive history associated with such experimental measurements (arguably, the first measurements of the velocities of ions in gases were carried out by Zeleny in Thompson's laboratory during early characterization of the properties of charged particles)⁴ and theory (rooted in Einstein's Ph.D. dissertation, which provides a mathematical description of the motion of large molecules diffusing through a bulk of smaller ones),⁵ the ability to resolve species in a mixture with similar mobilities remains limited. Generally, the resolving power ($R \equiv t_D / \Delta t$, where t_D is the ion's drift time and Δt is the full width of the peak at half-maximum) of IMS instruments is on the order of ~ 5 to 50^{6-11} for low resolution instruments, although several higher-resolution instruments capable of measurements with R = 100 to 240^{12-20} have been reported. In comparison, mass spectrometry resolving powers have improved much more rapidly; it is now routine to record an m/ Δm of 10⁴-10⁵, and higher values are obtainable by many research groups.21-27

Several years ago, Valentine and Clemmer proposed that if the resolving power of IMS measurements could be pushed to several thousand new information would become accessible.²⁸ Specifically, they predicted that the ability to resolve isotopic structure based solely on mobility measurements would allow one to develop information about ion mass directly from mobility measurements.²⁸ These ideas motivated us to consider new types of mobility measurements. In traditional IMS instruments, *R* scales as $(EL/T)^{1/2}$, where *L* is the drift region length, *E* is the magnitude of the applied drift field, and *T* is the buffer gas temperature.¹ Therefore, to improve the resolving power by a factor of 100, one would need to increase EL/T by a factor of 10^4 , which has proven to be experimentally challenging.

Because of these technical challenges, a number of other lesstraditional mobility-based measurement techniques are under development. Our group has developed overtone mobility spectrometry (OMS)^{29–33} and a cyclic drift tube^{34,36} with the aim of improving the resolution of species with similar mobilities. Shvartsburg and co-workers have dramatically improved field asymmetric waveform ion mobility spectrometry (FAIMS) measurements by a combination of factors that includes the use of nontraditional buffer gases.^{36–40} They have shown that the mobilities of amino acids, with identical nominal masses with different.⁴¹ Other efforts include the development of traveling wave ion mobility spectrometry (TWIMS),^{42–46} transversal modulation ion mobility spectrometry (TM-IMS),⁴⁷ trapped ion mobility spectrometry (TIMS),^{48,49} and differential mobility analysis (DMA).^{50–54}

In the present paper, we focus on improving IMS-based measurements using drift cells that utilize a cyclical configuration.^{34,35} Cyclical mobility measurements, which we sometimes call "ion cyclotron mobility spectrometry" (although we are not utilizing a magnetic field as found in typical cyclotrons⁵⁵), currently have limited utility as an analytical method because of the extremely low signals associated with a pulse of ions moving through many cycles of the drift region. In the present paper, we introduce an ion trapping approach that allows multiple pulses of ions to be accumulated in the cyclic drift tube prior to the initiation of IMS measurements. This

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allows us to study the dependence of the experimentally determined resolving power on cycle number. Overall, we find that increasing the separation cycle number improves the resolving power, and we have recorded values of R in excess of 1000. While the sensitivity of our measurements is still exceedingly low, the demonstration of improved resolving power is intriguing and has pushed us to try and understand this separation process in more detail. To this end, we have modeled the transmission and elimination of ions in the current cyclic drift tube design. A description of the experimental approach and insights gained from the modeling is given. Finally, the utility of the approach is demonstrated by examining a simple mixture of well studied ions with similar mobilities.

EXPERIMENTAL SECTION

General. Detailed descriptions of experimental configurations and theoretical treatments of IMS and scanning frequency OMS measurements are given elsewhere.^{1-3,16,17,29-35,56-64} The ion cyclotron mobility spectrometer, and an example of a typical pulsing sequence, used in these experiments are shown in Figure 1. For each experiment, the continuous ion beam formed from electrospray ionization⁶⁵ (ESI) was stored and accumulated in a Smith-geometry ion funnel^{15,66} (F1). An electrostatic gate (G1) was used to release packets of ions (150 μ s wide) into the drift region. The gating trigger is synchronized with a data acquisition system as well as the applied drift field frequency and exit gate (used to direct the motion of the ions around the cyclotron for additional cycles or fixed to release the ions from the cyclical drift tube and into mass analysis and detection regions). All of these features are described elsewhere.^{29-32,34,35}

Once the potential applied to G1 is lowered, ions move into the first segment of the cyclotron, a curved region which is referred to as the on ramp region (D1). From here, the ions enter the cyclical drift region, consisting of eight distinct segments: four curved regions (D1–D4) and four ion funnels (F2–F5). Each of the curved segments are 30.01 cm long, while each of the ion funnels are 15.21 cm long. After a fixed number of cycles, ions can exit the drift region through an off ramp region (D4). This region utilizes split lenses labeled as G2a and G2b, as shown in the inset in Figure 1. Slight differences in the voltages applied to these lenses make it possible for us to continue experiments for additional cycles around the cyclotron drift tube or release the packet for detection.

A home-built pulsing system (wavedriver)^{29,32,34,35} controls the drift field by generating square waves at a fixed frequency. The wavedriver applies potentials to the first and last lens of each segment while the drift field across each segment is established by a series of resistors (5 M Ω for each curve, 1.5 $M\Omega$ for each funnel) used as voltage dividers. The ions propagate around the cyclotron upon the administration of the first field application setting (phase A) with the injection pulse (G1). While phase A is applied, ions can move into D1, but a large repulsive potential that occurs between D1 and F2 prevents the movement of the ions into F2. Once the second field application setting (phase B) is applied, ions can then progress into F2, but a large repulsive potential prevents the movement of the ions into D2. Ions continue to propagate around the segments of the cyclotron with the oscillation of the field application settings in this manner.



Figure 1. Schematic diagram of the ion cyclotron mobility spectrometer used in these studies. The inset displays a blowup of the Y-shaped fork region labeled as D4, where G2a and G2b are electrostatic gates used to direct ions either around the cyclotron for additional cycles or fixed to release the ions to the detector for analysis. Reprinted from ref 35. Copyright 2010 American Chemical Society. The sequence of pulses applied to the source funnel (G1), the drift field wavedriver, and the electrostatic gates G2a and G2b are shown below the schematic. This represents an example of one complete injection sequence for ions that have been trapped for 1 3/4 cycles after four source pulses were introduced into the cyclotron. A more detailed description is provided in the text.

The circular portion has a DC drift field of approximately 8 $V \cdot cm^{-1}$ applied across each of the drift regions and ion funnels. The 32.35 cm linear region (D5 and F6) located after D4 uses higher fields; 9 V·cm⁻¹ for D5 and 11 V·cm⁻¹ for F6. F1 and F6 are operated with an RF of 530 kHz (115 V peak-to-peak (V_{p-p})) and 325 kHz (145 V_{p-p}), respectively. All other ion funnels (F2-F5) are operated with an RF of 250 kHz (175 V_{p-p}). Upon exiting the drift tube exit orifice, ions are focused through a series of ion optics before being mass analyzed and detected. The entire drift tube assembly is maintained at a pressure of 2.00 to 2.10 \pm 0.01 Torr He and 0.10 \pm 0.01 Torr N2. Nitrogen gas was introduced into the drift tube to prevent breakdown; although the drift voltage of the ions that are transmitted is low, more than 300 V·cm⁻¹ is applied across the ~ 1 cm wide junctions between segments (the region where ions are eliminated as shown below) in a given field application setting.

Electrospray Conditions. Individual solutions of the following peptides purchased from Sigma-Aldrich (St. Louis, MO) were used without further purification in 49:49:2 water/ acetonitrile/acetic acid by volume: human angiotensin II (93% purity, 2.4×10^{-4} M); substance P (95% purity, 1.8×10^{-4} M);

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bradykinin (98% purity, 2.4×10^{-4} M). A syringe pump (KD Scientific, Holliston, MA) was used to infuse solutions of one of the three peptides or a 1:1:1 mixture of the peptides through a pulled tip capillary biased 2350 V above the drift voltage.

RESULTS AND DISCUSSION

Simulations of Ion Motion under the Instrumental Conditions Employed. Simulations are conducted with a program written in-house and described in more detail elsewhere.^{16,30,31,33,67,68} The drift fields used to propagate ions around the cyclotron were generated using SIMION 8.0⁶⁹ in which the system was represented as a two-dimensional cross section of the lenses. The fields were then imported into the simulation program, where ion trajectories were calculated as a combination of directed and random diffusive motions. The directed motion of the ions is calculated from the mobility, while the diffusive motion is randomly determined from a Gaussian distribution with a standard deviation based upon the diffusion constant.² Directed motion is composed of two components, a DC component that is independent of time, and an RF component obtained from a time-dependent weighted averaging of two extremes of the applied RF. One field (E_{RF1}) was calculated when the applied RF voltages were at a maximum for every other lens while the intervening lenses were at a minimum. The second field (E_{RF2}) was calculated from the inverse situation, where the first set of lenses was at a minimum and the intervening lenses were at the maximum. A timedependent weighted average $(E_{RF} = E_{RF1}\sin(t) + E_{RF2}(1 - t))$ sin(t)), was used to calculate the field for each time step. For all simulations presented herein, the peak applied voltage was 150 V_{p-p} and the RF frequency was 450 kHz.

Individual simulations of the following ions were conducted: compact $[M + 3H]^{3+}$ ions of substance P, ions having a 30% greater mobility than the compact $[M + 3H]^{3+}$ ions of substance P, and $[M + 2H]^{2+}$ ions of substance P (approximately 30% lower mobility than the compact $[M + 3H]^{3+}$ ions of substance P). In order to demonstrate the range of possible behaviors for ions at different locations within the instrument, each simulation consisted of 60 duplicates for each of 2402 unique initial ion starting positions, for a total of 144 120 ions placed along the central axis throughout all eight segments of the cyclotron and representing the extreme of maximally dispersed packets. All of the simulations assume a pressure of 2 Torr, a temperature of 300 K, a time step of 0.25 μs , and a drift field application period (inverse of the drift field application frequency) of 2.34 ms.

Because we are interested in the location of the most stable packets of ions as they cycle the drift tube, we examined the location and movement of ions transmitting around the circle starting from one continuous packet of ions that spans the cyclic drift tube.^{30,31,68} The top, middle, and bottom rows in Figure 2 display snapshots of still-transmitting and eliminated ions taken for simulations at time points of 2.46, 3.39, and 18.60 ms, respectively. All of the 144 120 ions simulated were included for each of the snapshots displayed in Figure 2. The left, center, and right columns correspond to ions that have mobilities 30% higher, matched, and 30% lower, respectively, than that of the 2.34 ms drift field application period. As the simulation progresses, we observe trapping of mobility-selected ions and elimination of portions of the continuous ion distribution; this eventually yields four discrete packets, as shown for all three time points displayed in Figure 2.



Figure 2. Snapshots of the trajectory of ions traveling two cycles around the cyclotron are plotted for three time points: 2.46, 3.39, and 18.60 ms. The left, center, and right columns correspond to ions with a 30% higher mobility than the compact $[M + 3H]^{3+}$ ions of substance P, matched mobility ions (compact $[M + 3H]^{3+}$ ions of substance P), and 30% lower mobility ions ($[M + 2H]^{2+}$ ions of substance P) at a drift field application period of 2.34 ms. Lenses of the cyclotron are shown in black, eliminated ions are in red, and transmitting ions are in blue.

Signal Enhancement of Mobility-Selected Ions. The observation of four stable packets spaced equally around the cyclic drift tube led us to enhance ion signals by introducing ions into the circular drift tube at times corresponding to the location of the stable transmittable ion packets. Previously, we have periodically introduced a single discrete packet of ions from the source into the cyclotron at the initiation of every experiment.^{34,35} This allowed a limited number of ions into the cyclotron that were capable of traveling multiple cycles around the instrument. The number of ions that can propagate numerous cycles around the cyclotron in a given experiment can be increased with the introduction of a large packet of ions from the source.

To determine the enhancement in signal that can be achieved, we first scanned the drift field application frequency in order to find the frequency at which ion signal is maximized for compact $[M + 3H]^{3+}$ ions of substance P. The resulting drift field application frequency was found to be 306.75 Hz for ions that traveled 20 3/4 cycles around the instrument with a 150 μ s wide source pulse. We then recorded ion intensity as a function of the width of the source pulse. These data are shown in Figure 3. As expected, these data show that ion signals increase with increasing source width; examination of the total drift time distribution as a function of source width shows that at short pulse times (i.e., 150 μ s) a single pulse of ions emanates from the drift tube. This is consistent with filling only one of the four stable regions of the cyclotron with the short pulse. As this pulse increases, the steps in the ion intensity show that additional regions can be utilized (and additional peaks are emitted from the drift tube) as shown in Figure 3.

Once the first drift region segment is full, the signal remains relatively constant until the next segment begins to fill. Similarly, when the second, third, and fourth segments are each filled, limited improvement is obtained until additional drift regions are accessible. Under typical conditions, the cyclotron region appears to have reached capacity upon accumulation of ions for three to four cycles. At these longer



Figure 3. Intensity as a function of the source pulse width for ions that have experienced 20 3/4 cycles around the cyclotron at a drift field application frequency of 306.75 Hz. Source pulse widths were 150 μ s and from 500 to 50 000 μ s in increments of 500 μ s. Widths that correspond to overlap with additional segments of the cyclotron are shown in red. Example drift time distributions are provided to show the additional peaks that are observed upon the sequential filling of individual segments of the cyclotron obtained with the following source pulse widths: 150, 3000, 6500, 9500, and 12 000 μ s.

filling times, we still observe four discrete peaks in the drift time distributions, indicating that ions are transmitted as four stable regions.

When using multiple discrete injection packets, ions may travel farther than the minimum distance, we define the number of trapped cycles to be the number of cycles an ion travels around the cyclotron after the last source pulse was introduced into the cyclotron. As an example, when trapping ions for 60 3/ 4 cycles, increasing from the injection of one source pulse (in a time corresponding to one fourth of a cycle) to eighty source pulses (corresponding to the time of 20 cycles) increases the duty cycle from 0.4% to 25%.

Resolving Power with Increasing Number of Drift Cycles. With the introduction of trapping techniques, it becomes possible to investigate the ability to resolve peaks at higher cycle numbers; with a single pulse under ideal conditions, we are able to examine ions to a maximum ~ 60 cycles. Figure 4 displays the resulting drift field application frequency distributions obtained for the compact $[M + 3H]^{3+}$ ions of substance P with 2.00 Torr He and 0.10 Torr N2 that have been trapped for 60 3/4, 70 3/4, 80 3/4, 90 3/4, and 100 3/4 cycles; we note that on rare occasions we have transmitted ions through greater distances but these data cannot be obtained routinely. Therefore, we do not discuss these results further here. For each distribution, 28 source pulses each with a width of 150 μ s and a period equal to the drift field application frequency were released into the cyclotron at the initiation of a given experiment. The injection of 28 pulses corresponds to the introduction of 7 cycles of pulses into the cyclotron (to ensure that we are near capacity), which requires the ions from the first source pulse to travel 67 3/4, 77 3/4, 87 3/4, 97 3/4, and 107 3/4 cycles, and resulted in 60 3/4, 70 3/4, 80 3/4, 90 3/4, and 100 3/4 cycles trapped within the cyclotron after the ion



Figure 4. Drift field application frequency distributions are shown for the compact $[M + 3H]^{3+}$ ions of substance P that have traveled 60 3/4, 70 3/4, 80 3/4, 90 3/4, and 100 3/4 cycles around the cyclotron. A resolving power of approximately 1040 was obtained for ions that have traveled 100 3/4 cycles around the cyclotron, which corresponds to a total drift length of 182.86 m.

introduction process was completed. Examination of these peaks shows that the resolving power continues to increase at high-cycle number. For the compact $[M + 3H]^{3+}$ ions of substance P, we obtain R values of 297, 361, 415, 780, and 1040 when ions are studied at 60 3/4, 70 3/4, 80 3/4, 90 3/4, and 100 3/4 cycles, respectively. As a point of reference, ions that have undergone 100 3/4 cycles travel at least 182.86 m.

Example Illustrating the Ability to Resolve Closely **Spaced lons.** With accessibility to such high resolving power, it is interesting to examine a set of ions with very similar mobilities. We have chosen three triply charged peptides with similar cross sections that were determined previously using a helium buffer gas: angiotensin II (having $\Omega = 292$ Å²),⁷⁰ bradykinin (having $\Omega = 304$ Å², conformation C),⁷¹ and substance P (having $\Omega = 320$ Å², compact).⁷² In order to resolve all three of these ions at half height, we calculate that R \geq 25 is required; baseline resolution with multiple conformers requires even higher R. For reference, drift field application frequency distributions for each of these three ions are shown in Figure 5 (individually as well as a mixture) at 20 3/4 cycles. Clearly, at 20 3/4 cycles, the mixture of components remains unresolved. At 90 3/4 cycles, three peaks were easily resolved and assigned to the individual peptides within the mixture based on the drift field application spectra observed at 20 3/4 cycles. We note that while the ordering of these three peaks (321.96, 314.07, and 306.64 Hz for angiotensin II, bradykinin, and substance P, respectively) is consistent with the inverse order of the measured cross sections in helium, our present results are obtained in a mixture of nitrogen and helium; thus, we do not report absolute cross sections from these data.

CONCLUSIONS

We have described, modeled, and demonstrated a new ion trapping technique to accumulate ions within a cyclical drift tube to increase ion signals. With this approach, multiple packets of ions were released into the drift tube at the initiation



Figure 5. Drift field application frequency distributions for three individual peptides ((a) angiotensin II (Ang II), (b) bradykinin (Bk), and (c) substance P (sub P)) that have traversed 20 3/4 cycles around the cyclotron and for a 1:1:1 mixture of angiotensin II, bradykinin, and substance P ions that after (d) 20 3/4 and (e) 90 3/4 cycles of trapping. A regression of collision cross sections against the drift field application period for these three peptides was used to assign the main feature for the $[M + 3H]^{3+}$ ions of bradykinin to the conformation previously denoted as C. Three peak apexes can be observed in the inset at 20 3/4 cycles for the $[M + 3H]^{3+}$ ions of bradykinin, and compact $[M + 3H]^{3+}$ ions of substance P occurring over a drift field application frequency range of 280 to 350 Hz. The inset at 90 3/4 cycles displays the resulting drift field application frequency distribution obtained from the same mixture, in which the species are resolved.

of a given experiment, effectively creating a mobility-selective ion trap. The enhancements in ion signals obtained with the utilization of this ion trapping technique has allowed us to observe ions that have traveled over 100 cycles around the cyclotron where a resolving power in excess of 1000 was achieved for the compact $[M + 3H]^{3+}$ ions of substance P without leaving the low-field regime. With this resolving power, we were able to separate a mixture of three peptides with similar mobilities: angiotensin II, bradykinin, and substance P. We note that while the improvements in these techniques are encouraging these experiments are still at an early stage and ion signals are quite limited. We are currently in the process of improving ion transmission in this system.

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Notes

The authors declare no competing financial interest.

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