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Single Field Direct Drift
Time to CCS Calibration
for a Linear Drift Tube Ion
Mobility Mass
Spectrometer

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Introduction

Ion mobility (IM) spectrometry is a gas-phase ion separation technique in which ions become separated in time as they travel through a drift cell of known length containing a buffer gas (drift gas). During this travel, the ions become separated based on their mobilities, which can be correlated to their unique collision cross section values (CCSs) through the buffer gas. An IM system in general includes an ion source for ionizing molecules of a sample of interest, followed by the drift cell that receives the ions, followed by an ion detector for counting the separated ions. The ion detector communicates with electronics configured for processing output signals from the ion detector as needed to produce a user-interpretable drift spectrum. The drift spectrum is typically presented as a plot containing a series of peaks indicative of the relative abundances of detected ions as a function of their drift time through the drift cell. The drift spectrum may be utilized to identify and distinguish different analyte species of the sample.

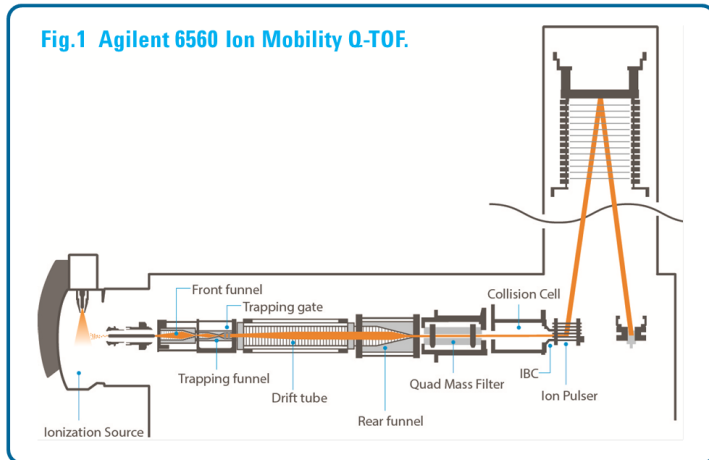
IM may be coupled with one or more other types of separation techniques to increase compound identification power, such as liquid chromatography (LC), or mass spectrometry (MS). For example, an IM drift cell may be coupled in-line with an MS system to form a combined IM-MS system. An IM drift cell is often coupled to a time-of-flight mass spectrometer (TOF MS), for example, see Fig 1. for the instrument of the present study.

In the combined IM-MS system, the ion source is followed by the IM drift cell, which is followed by the mass analyzer and then the ion detector. Typically in drift-time IM techniques, ions travel through the drift cell under the influence of a uniform DC voltage gradient established by electrodes of the drift cell. While the electric field moves the ions through the drift cell, the ions experience a drag force due to collisions with the stationary buffer gas molecules in the drift cell. After entering the drift cell, an equilibrium state between the drag force and electrical force is quickly reached and the ions start moving with constant drift velocity V_d , which is proportional to the applied electric field of strength E as follows:

$$V_d = KE,$$

where the proportionality constant K is the gas phase mobility of an ion.

Fig.1 Agilent 6560 Ion Mobility Q-TOF.



Thus, the mobility of an ion of interest may be calculated experimentally by measuring the ion's velocity or drift time t_d , i.e., the time taken by the ion to traverse the drift cell of known length L and applied electric field strength E .

If the drift time of an ion through the drift cell, the pressure in the drift cell, and the voltage across the drift cell are known, then one can calculate the CCS of the ion. This CCS parameter is specific for the ion and is instrument-independent, and therefore can be utilized as a unique parameter for compound identification. The absolute CCS may be calculated directly from experimentally determined variables by Mason-Schamp equation, as follows:

$$\Omega = \frac{(18\pi)^{1/2}}{16} \frac{qe}{(k_b T)^{1/2}} \left[\frac{1}{m_I} + \frac{1}{m_B} \right]^{1/2} \frac{t_d E}{L} \frac{760}{P} \frac{T}{273.2} \frac{1}{N}$$

However, in a typical IM based system, there is some distance over which an ion travels from the exit of the drift cell to the ion detector. Thus, the observed drift time of an ion as measured by the detector, t_D , is greater than the actual time the ion took to travel through the drift cell, t_d . The drift time t_d utilized in the Mason-Schamp equation to calculate the CCS of the ion is a "corrected" drift time, which may be found from the following relation:

$$t_d = t_D - t_0,$$

where t_0 is the time the ion spent traveling from the exit of the drift cell to the ion detector. The proper calculation of time t_0 is crucial for the accuracy of CCS measurements.

Theoretical Analysis

Conventionally, time t_0 is calculated by performing several IM experiments at different drift field strengths, E (V/cm) and plotting observed (measured) drift time t_D (y-axis) over the inverse of the applied drift voltage ($1/V$) (or over field strength ($1/E$)) (x-axis). The resulting plot is a set of data points ($1/V$, t_D) lying along a straight line showing the linear correlation between observed drift time and inverse applied drift field/voltage. The intercept of this plot with the y-axis (drift time axis) is the time t_0 for the ion of interest.

The common practice is to employ at least five different drift voltages for one CCS experiment. Unfortunately, such an amount of measurement time is unacceptably long for many situations.

Therefore, there is a need for providing a method for faster CCS measurement, particularly one that is compatible with the time scale of chromatographic separation.

The time t_0 , during which an ion spends outside the drift cell may be considered as including two components: a fixed delay time and an external (outside the drift cell) mobility-dependent drift time, which may be expressed as follows:

$$t_0 = t_{fix} + \beta_1 \gamma \Omega,$$

where t_{fix} is the fixed delay time parameter, and $\beta_1 \gamma \Omega$ is the external mobility-dependent time. The value β_1 is a proportionality coefficient dependent on the gas pressures in the system, electrical fields, and geometry of the regions of the system outside the drift cell. The value γ is a modified reduced mass coefficient, $\gamma = (m_1 / (m_1 + m_B))^{1/2} / q$. Consequently, the total measured (observed) drift time of an ion, t_D , is considered to include three components: the fixed delay time parameter, the external mobility-dependent drift time and an internal mobility-dependent time (i.e., the time actually taken by the ion to traverse the interior of the drift cell from entrance to exit). The total measured drift time t_D may be expressed as follows:

$$t_D = t_{fix} + ((\beta_1 + \beta_2) \gamma \Omega), \quad (1)$$

where $\beta_2 \gamma \Omega$ is the drift time in the drift cell (internal mobility-dependent time), and β_2 is a proportionality coefficient dependent on the gas pressure, electrical field, and geometry of the drift cell itself.

From equation (1) it is seen that plotting total measured drift time t_D values (y-axis) versus $\gamma \Omega$ values (x-axis) produces a straight line defined by two parameters, t_{fix} and $\beta = (\beta_1 + \beta_2)$, where β is the slope and t_{fix} is the y-intercept as defined by the following equation:

$$t_D = t_{fix} + \beta \gamma \Omega, \quad (2)$$

The β -parameter is an instrument-dependent proportionality coefficient.

The two parameters t_{fix} and β may be determined by acquiring reference data points ($\gamma \Omega$, t_D) from a group of reference ions having known CCSs, and performing a simple linear regression technique on the plot (equation (2)) of the reference data points.

Experimental

A high resolution IM-QTOF (Agilent Technologies, 6560 IM-QTOF) instrument was used in this study (Fig. 1). All chromatography was performed on Agilent 1290 LC. Details of the experiments are shown on the caption for Fig. 2.

Conclusions

A novel high speed technique is developed for calibration of the CCS domain for a linear drift IM-MS spectrometer

The technique allows fast and routine CCS measurements in a single LC run with pre/post or in-run calibration

Current technique requires to have info on both m/z and z of an ion to identify its CCS based on the CCS of two known ions and therefore it is perfectly matching IM to MS tandem instrumentation

This approach makes mobility dimension to become similar to m/z dimension but with CCS values. Both m/z and CCS info can be obtained essentially at the same time using current technique

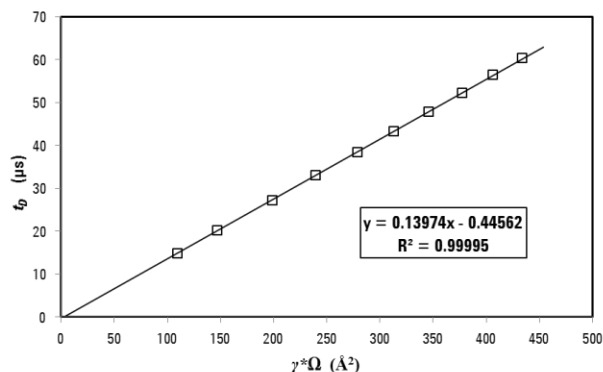
The technique is implemented on Agilent 6560 IM-QTOF with Mass Hunter software for automated feature finding and CCS calculations

Results and Discussion

EXAMPLE 1 (Agilent Calibration mix - CCS measurements)

CCS ref. compound	m/z	CCS (Å ²), referenced	drift time t_D (ms)
1	118	121.5	14.86
2	322	153.4	20.2
3	622	202.4	27.24
4	922	242.7	33.01
5	1222	280.9	38.39
6	1522	315.7	43.22
7	1822	348.6	47.78
8	2122	379.8	52.16
9	2422	408.3	56.36
10	2722	435.7	60.32

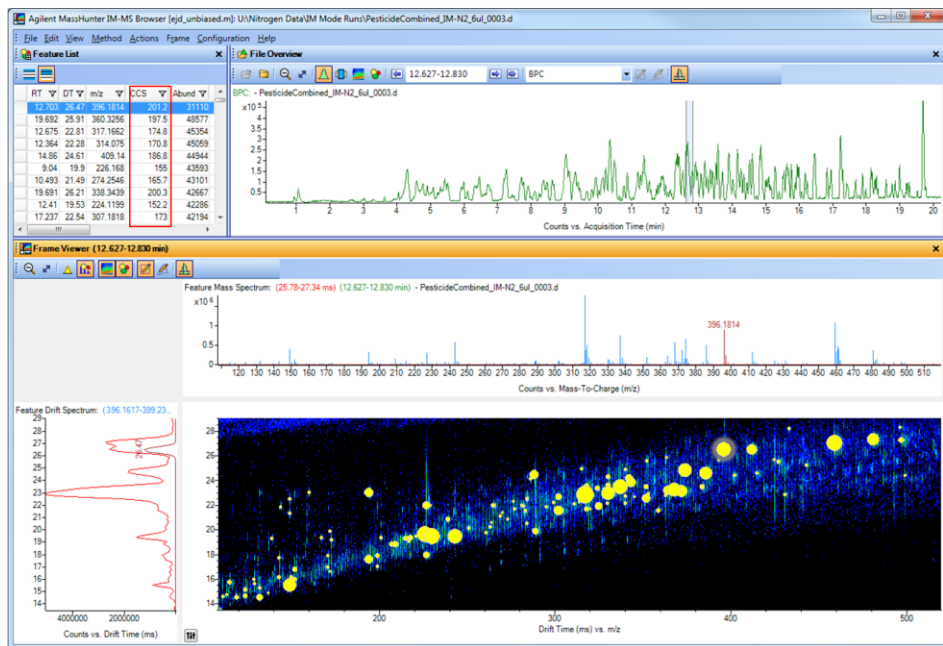
Fig.2 is the CSS calibration plot of t_D vs. $\gamma\Omega$ for the reference compounds in nitrogen. R^2 value with .9999 is achieved



Compound	m/z	drift time (ms)	CCS (Å ²), literature referenced	CCS (Å ²), calculated	Error, %
Colchicine	400.44	25.99	196.2	196.9	0.27
Ondansetron	294.40	22.62	173.2	173.4	0.26

To evaluate the calibration, two additional compounds with known CCSs were infused immediately after the ten reference compounds and their drift times were measured. Using the values found for β and t_{fix} , the CCSs of these two compounds were calculated according to the method described above. Less than 1% deviation from literature data are observed.

EXAMPLE 2 (Hundred Pesticide Mix LC IM-MS analysis)



The upper plot shows a base peak chromatogram of the entire LC separation.

The plot below shows an average mass spectrum from the retention time range 12.6-12.8 minute.

The bottom panel shows an abundance map of the data at the same retention time.

Yellow dots mark the location of ions ("features") included in the feature list table.

The MassHunter software calculates CCS values (marked with red box) automatically for all of the features listed in the table.